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What empirical research has been undertaken on the ethics of clinical research in India? A systematic scoping review and narrative synthesis

Paramasivan, Sangeetha ; Davies, Philippa ; Richards, Alison ; Wade, Julia ; Rooshenas, Leila ; Mills, Nicola ; Realpe, Alba ; Raj, Jeffrey Pradeep ; Subramani, Supriya ; Ives, Jonathan ; Huxtable, Richard ; Blazeby, Jane M ; Donovan, Jenny L

Abstract: IntroductionThe post-2005 rise in clinical trials and clinical research conducted in India was accompanied by frequent reports of unethical practices, leading to a series of regulatory changes. We conducted a systematic scoping review to obtain an overview of empirical research pertaining to the ethics of clinical trials/research in India.MethodsOur search strategy combined terms related to ethics/bioethics, informed consent, clinical trials/research and India, across nine databases, up to November 2019. Peer-reviewed research exploring ethical aspects of clinical trials/research in India with any stakeholder groups was included. We developed an evidence map, undertook a narrative synthesis and identified research gaps. A consultation exercise with stakeholders in India helped contextualise the review and identify additional research priorities.ResultsTitles/Abstracts of 9699 articles were screened, full text of 282 obtained and 80 were included. Research on the ethics of clinical trials/research covered a wide range of topics, often conducted with little to no funding. Studies predominantly examined what lay (patients/public) and professional participants (eg, healthcare staff/students/faculty) know about topics such as research ethics or understand from the information given to obtain their consent for research participation. Easily accessible groups, namely ethics committee members and healthcare students were frequently researched. Research gaps included developing a better understanding of the recruitment-informed consent process, including the doctor-patient interaction, in multiple contexts and exploring issues of equity and justice in clinical trials/research.ConclusionThe review demonstrates that while a wide range of topics have been studied in India, the focus is largely on assessing knowledge levels across different population groups. This is a useful starting point, but fundamental questions remain unanswered about informed consent processes and broader issues of inequity that pervade the clinical trials/research landscape. A priority-setting exercise and appropriate funding mechanisms to support researchers in India would help improve the clinical trials/research ecosystem.

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BMJ Global Health

What empirical research has been undertaken on the ethics of clinical research in India? A systematic scoping review and narrative synthesis

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ABSTRACT

Introduction The post-2005 rise in clinical trials and clinical research conducted in India was accompanied by frequent reports of unethical practices, leading to a series of regulatory changes. We conducted a systematic scoping review to obtain an overview of empirical research pertaining to the ethics of clinical trials/research in India.

Methods Our search strategy combined terms related to ethics/bioethics, informed consent, clinical trials/research and India, across nine databases, up to November 2019. Peer-reviewed research exploring ethical aspects of clinical trials/research in India with any stakeholder groups was included. We developed an evidence map, undertook a narrative synthesis and identified research gaps. A consultation exercise with stakeholders in India helped contextualise the review and identify additional research priorities.

Results Titles/Abstracts of 9699 articles were screened, full text of 282 obtained and 80 were included. Research on the ethics of clinical trials/research covered a wide range of topics, often conducted with little to no funding. Studies predominantly examined what lay (patients/public) and professional participants (eg, healthcare staff/students/faculty) know about topics such as research ethics or understand from the information given to obtain their consent for research participation. Easily accessible groups, namely ethics committee members and healthcare students were frequently researched. Research gaps included developing a better understanding of the recruitment-informed consent process, including the doctor-patient interaction, in multiple contexts and exploring issues of equity and justice in clinical trials/research.

Conclusion The review demonstrates that while a wide range of topics have been studied in India, the focus is largely on assessing knowledge levels across different population groups. This is a useful starting point, but fundamental questions remain unanswered about informed consent processes and broader issues of inequity that pervade the clinical trials/research landscape. A priority-setting exercise and appropriate funding mechanisms to support researchers in India would help improve the clinical trials/research ecosystem.

Key questions

What is already known?

- The increase in the number of clinical trials and clinical research conducted in India after 2005 was accompanied by many reports of ethical misconduct, with bioethics reports and health activism prompting a series of regulatory changes by the government.
- While there was a corresponding increase in empirical research on various ethical aspects of clinical trials/research in India, little was known about the scope of this research or what areas of research required further attention to improve the clinical trials/research ecosystem.

What are the new findings?

- Research on ethical aspects of clinical trials/research in India was often carried out with limited to no funding, covered a wide range of topics but with a focus on knowledge assessments of lay and professional groups on topics such as research ethics, and leaned on easily accessible groups such as ethics committee members and healthcare students for study populations.
- A range of research gaps were identified, facilitated by a consultation exercise with key stakeholders from India, and included developing a better understanding of the different components of the recruitment and informed consent process, such as the doctor-patient interaction, developing models of informed consent specific to the Indian context and exploring issues such as equity and justice within the context of clinical trials/research.

INTRODUCTION

International clinical trials recruit participants from low-income and middle-income countries (LMICs) for economic, pragmatic and scientific reasons.[1] Post-2005, when the World Trade Organisation-Trade Related Intellectual Property Rights agreement

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What do the new findings imply?

- There is a need to move from knowledge assessments towards addressing other fundamental questions about recruitment, informed consent, equity and justice.
- The large number of research gaps identified warrants a locally led priority-setting exercise as well as appropriate funding mechanisms to support researchers in India to undertake clinical trials/research methodology and ethics-related research.

became fully binding for India, the number of clinical trials approved by the Indian government's regulatory authority, Central Drugs Standard Control Organisation, began to increase,[2] peaking in 2010 followed by a sharp decline to 2013[3] (online supplemental file 1). An identical pattern of growth and contraction was observed in India's clinical trial sector's growth rate, in research using clinicaltrials.gov data.[4]

The downward trend is attributed to the chain of events that began with unacceptable ethical practices, such as failure to obtain participants' informed consent for trial participation,[5] being reported nationally and internationally.[6–11] In 2013, the Supreme Court of India intervened and briefly halted approvals for new clinical trials[12] in response to concerns for participant autonomy and safety, and public interest litigations from non-governmental organisations.[13 14] New regulations were introduced in 2013 as amendments to Schedule Y of the Drugs and Cosmetics Rules 1945,[15] mandating measures such as registration of ethics committees[16] and audio-visual (AV) recordings of the informed consent discussion,[17 18] the latter being a requirement that is unique to India (see Gogtay *et al*[18] for an overview of regulatory changes/requirements in India from 2005 to 2016). Also specific to India is that the term 'clinical trial' is limited to the study of 'new drugs' only, with Biomedical and Health Research (BMHR) referring to all other basic, applied, operational and clinical research[19] (in contrast to broader definitions of 'clinical trial', which include medical, surgical and behavioural interventional research).[20 21] The most recent regulatory changes outlined in the New Drugs and Clinical Trial (NDCT) Rules of 2019[19 22] bring non-drug-related research (ie, BMHR) within the regulatory ambit for the first time[19 23] (previously, regulatory mechanisms in India were principally focused on 'new drug' research). The NDCT Rules[19] also separate the ethics and governance processes for clinical trials and bioavailability/bioequivalence studies from those for BMHR studies. For instance, two different types of ethics committees, each with separate authorities responsible for their registration and monitoring, will approve the two groups of studies. It is also now mandatory for BMHR ethics committees and academic clinical trials to adhere to the Indian Council for Medical Research's National Ethical Guidelines for Biomedical and Health Research Involving Human Participants.[24 25]

Given this backdrop, there is a large body of theoretical bioethics literature and commentary by researchers, advocacy groups and bioethicists, covering topics such as lessons learnt from conducting clinical trials,[26–28] 'standard care' in clinical trials,[29 30] structure of the clinical trial industry,[31] informed consent placed within the wider socioeconomic context,[32] role of ethics committees[33] and ensuring appropriate compensation mechanisms.[34] There has also been a corresponding increase in empirical research on the ethics of clinical trials specifically and clinical research more broadly (henceforth clinical trials/research) in India, which has not been comprehensively reviewed. We therefore sought to summarise this body of research evidence through a systematic scoping review and narrative synthesis to help identify research gaps.

METHODS

We undertook a systematic scoping review following the established six-step framework by Arksey and O'Malley,[35] drawing from recommendations to enhance the methodology[36–38] and adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for scoping reviews[39] (online supplemental file 2).

An initial systematic review of clinical trial informed consent interventions in India (PROSPERO registration: CRD42017068966) was amended to a systematic 'scoping' review (not within PROSPERO's remit, hence withdrawn) of research on the ethics of clinical trials/research in India, as the latter method is particularly useful when the aim is to map the evidence base in a broad but complex unreviewed area.[35 37 38]

Identifying the research question

We sought to obtain an overview of the empirical evidence in relation to the ethics of conducting clinical trials/research in India. More specifically, we aimed:

a. to map the empirical research undertaken on any ethical aspect of conducting clinical trials/research in India;
b. to synthesise the key themes from this evidence base, with a focus on informed consent;
c. to identify gaps to inform future research priorities.

Identifying relevant studies

Inclusion criteria

The research questions were assessed in relation to the setting, population, phenomenon of interest and the study design of articles (online supplemental file 3). We included articles that reported (a) on original research in a peer-reviewed journal, (b) on India as a country for data collection (if study involved many countries, included if India-specific findings could be differentiated), (c) on ethical issues in relation to clinical trials/research and (d) with any key stakeholder groups—lay (public; clinical trials/research participants; patients/guardians), professional (healthcare/research faculty, students or practitioners; ethics committee members;

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regulatory/governmental agencies) or documents (informed consent forms; ethics applications).

Exclusion criteria

We excluded commentaries, 'lessons learnt' articles, abstracts, letters, audits (eg, Clinical Trials Registry-India audits,[40 41] except when linked to an ethical issue), and studies from countries other than India (eg, studies exploring views of researchers from high-income countries undertaking research in LMICs).[42 43] We excluded studies on the following topics:

a. Willingness to participate (WTP) in clinical trials/research and recruitment-focussed studies, except when they considered ethical issues (there are other systematic reviews on WTP[44–46]; WTP components of included studies were not considered in this review).
b. Informed consent/ethical issues in relation to procedures/treatment outside of clinical trials/research (eg, in routine surgery).[47 48]
c. Pharmacovigilance (PV) studies (there are systematic reviews on PV[49]; PV components of included studies were not considered in this review).
d. Other: studies on medical/healthcare/clinical ethics (ie, not in relation to clinical trials/research or research ethics) and research skills/capacity with professional groups (eg, healthcare students).[50 51]

No restrictions were applied based on language, age (children/adult), study design or quality of research.

Search strategy

We searched the following nine electronic bibliographic databases with no start date and up to 5 September 2017 and this was updated using the technique by Bramer and Bain[52] to 12 November 2019: MEDLINE, Cochrane Library, Web of Science, Scopus, Embase, PsycINFO, Cumulative Index of Nursing and Allied Health Literature, International Bibliography of Social Sciences and Online Resource for Recruitment research in Clinical TriAls.[53] Search terms relating to three domains were combined: (a) ethics, bioethics, informed consent; (b) clinical trials/research and (c) India. A comprehensive search strategy first developed on MEDLINE (SP) drew from systematic reviews on related topics,[54 55] was refined by an information specialist (ARi) and adapted to the other databases (online supplemental file 4—MEDLINE search strategy). Searches included other South Asian countries to gather contextual information, but the review focused on India. We used a combination of Medical Subject Headings, text word searches and search strings using proximity indicators. We searched the reference lists of eligible research articles and ineligible key opinion/commentary pieces, and contacted authors of published conference abstracts to trace studies.

Study selection

All articles identified from the databases and other sources were downloaded to EndNote-X9[56] and duplicates removed. Following the original search in September 2017, one reviewer (SP) screened the titles and abstracts of all articles with a 20% random sample screened independently by a second reviewer (PD). There was a high level of agreement across the two reviewers (disagreement in 3 of 1292 articles), with discrepancies discussed and resolved. Full text of all relevant articles were obtained and screened independently by at least two authors (SP with NM, JW, LR). Discordance was again resolved through group discussion among all four reviewers. Where it was unclear if an article or a particular topic should be included (eg, biobanking, data sharing), a decision was made by meeting with two content experts (ethicists JI and RH) and reviewing the articles together. For the search and screening update in November 2019, SP carried out all steps.

Charting the data: data extraction and quality assessment

A data extraction form was developed (SP) and independently applied by two reviewers (SP and ARe) on a sample of articles (n=10). The form was refined after discussion and captured the following information (SP, ARe, JPR, SS): authors, year of publication and data collection, location, study aim, topic area, population, study design/methods, participants and findings. Subsequently, further information was captured on (SP): (a) whether studies were conducted within the context of a real or hypothetical study/scenario and (b) whether they explored broad (eg, clinical trials/research, research ethics) or specific topics (eg, data sharing, compensation).

Two review authors (SP with LR, JW, PD, JPR, SS) independently assessed the quality[57] of the majority of studies using the following tools: Critical Appraisal Skills Programme (CASP) checklist[58] for qualitative studies; Appraisal tool for Cross-Sectional Studies (AXIS; adapted to have 14 items instead of 20)[59] for quantitative studies and AXIS, CASP and a section of the Mixed Methods Appraisal Tool[60] for mixed methods studies. Quality assessments were discussed to resolve discrepancies and used to summarise relevant methodological issues in the narrative synthesis.

Collating, synthesising and reporting the results

We first quantified the data in relation to the study characteristics. Next, we created an evidence map to visualise the volume of studies by topic, population group and methods. Finally, we synthesised the quantitative and qualitative findings reported in included studies, using EndNote-X9[56] for data management and MaxQDA-12[61] for coding articles, and used narrative and thematic description to write detailed descriptive accounts. The synthesis broadly followed the categorisations in the evidence map, but looked across all included articles to provide a comprehensive account of research on a given topic.

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Consultation

The consultation phase, considered optional in scoping reviews,[35] took place after the synthesis, with the aim of informing the review and ensuring local priorities and context were accounted for. We approached colleagues in India who were researchers, ethicists and representatives from advocacy groups, through prior networks or because they had authored seminal empirical and/or conceptual papers (online supplemental file 5—consultation members). Consultation was carried out via virtual conferencing, email and telephone. Findings and research gaps identified through the review were discussed. Key recommendations made by stakeholders were grouped by topic and incorporated in the manuscript, tables or supplements.

Patient and public involvement

No patients or members of the public were involved in this review.

RESULTS

Description of included studies

A total of 9699 unique records were identified (original, updated and manual searches), of which 282 full-text articles were assessed against the inclusion/exclusion criteria and 80 included[62–141] (figure 1). Key study characteristics are summarised in table 1 (individual study details are in online supplemental file 6).

Most studies were conducted in urban settings (47/80), in the western (24/80) and southern (21/80) parts of India. Studies were mainly quantitative (60/80), questionnaire surveys (36/60), conducted with professional groups (34/80) and appeared in journals published in India (49/80), primarily the *Indian Journal of Medical Ethics*[142] and *Perspectives in Clinical Research*[143] (n=15 and 16, respectively).

There were no research studies published on the ethical issues around conducting clinical trials/research until 2008, with a large proportion published a few years before and after the landmark regulatory changes of 2013 (53/80 were published 2011–2016; online supplemental file 1). Many studies did not mention the year of data collection (27/80) and of those that did, only a few were carried out in/after 2013 (17/53).

Corresponding authors of most studies were based within academic institutions (69/80; 15 outside India and 54 within India), primarily within Departments of Pharmacology of various Indian institutions (24/54). Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai had the most number of corresponding authors (12/54), followed by Christian Medical College, Vellore (5/54). Two-thirds of studies (53/80) did not provide information on their funding source (26/53) or stated they did not receive any funding (27/53); of the remaining, 21 were funded/supported by international grants, 4 by intramural grants and 2 by pharmaceutical companies. There was no statement on conflicts of interest in 28 studies.

Evidence map: research on ethical aspects of conducting clinical trials/research in India

We developed an evidence map that charts the total articles included (n=80) by the main focus of the topics and population covered in the studies, alongside the methods used (table 2).

Primary research (n=58): more than half (32/58) were studies exploring knowledge (with or without attitude and practice components) of participants on topics such as information provided to obtain informed consent (primarily with lay participants), clinical trials/research, research ethics and ethics committees (primarily with professional participants), and were mainly quantitative (27/32). Studies that assessed comprehension of the informed consent form or verbal information provision (n=10) were carried out in real (8/10) and hypothetical (2/10) randomised controlled trials (RCTs), clinical trials and cohort studies.

Another large group of primary research studies (26/58) focused on perceptions, experiences and practices/processes on topics such as the extent of patient participation in informed consent discussions, AV recording of consent processes, ethics committees, research governance (eg, data sharing) and the larger clinical trials landscape in India (such as outsourcing, contract research organisations and civil society organisations). Studies employed a wider range of methods (11 quantitative, 13 qualitative studies, 2 mixed methods) and some (9/26) were conducted in the context of a real and/or hypothetical study.

Secondary research (n=22): these studies were all quantitative and were centred around documentary reviews of the quality of application forms submitted to ethics committees, compliance of informed consent documents to guidelines/regulations, and Indian journal articles' reporting practices on informed consent and ethical approval.

Narrative synthesis: key findings and research gaps

The findings from included studies were synthesised based on population groups (lay/professional) and key topic areas, with summaries of methodological issues where relevant. Sections A1–A6 and B1 indicated below correspond to those in table 3, which highlights the key findings from the synthesis alongside identified gaps (see online supplemental file 7 for full report of synthesis).

Primary research was synthesised in six key areas (A1–A6). The first four (A1–A4) covered studies that involved comprehension of the informed consent form and knowledge of clinical trials/research, research ethics and ethics committees (where attitudes and/or practices were reported, these were synthesised). Research on informed consent processes (A5) and broader cross-cutting themes that provided a more holistic understanding of the clinical trials industry (A6) were also synthesised. Secondary

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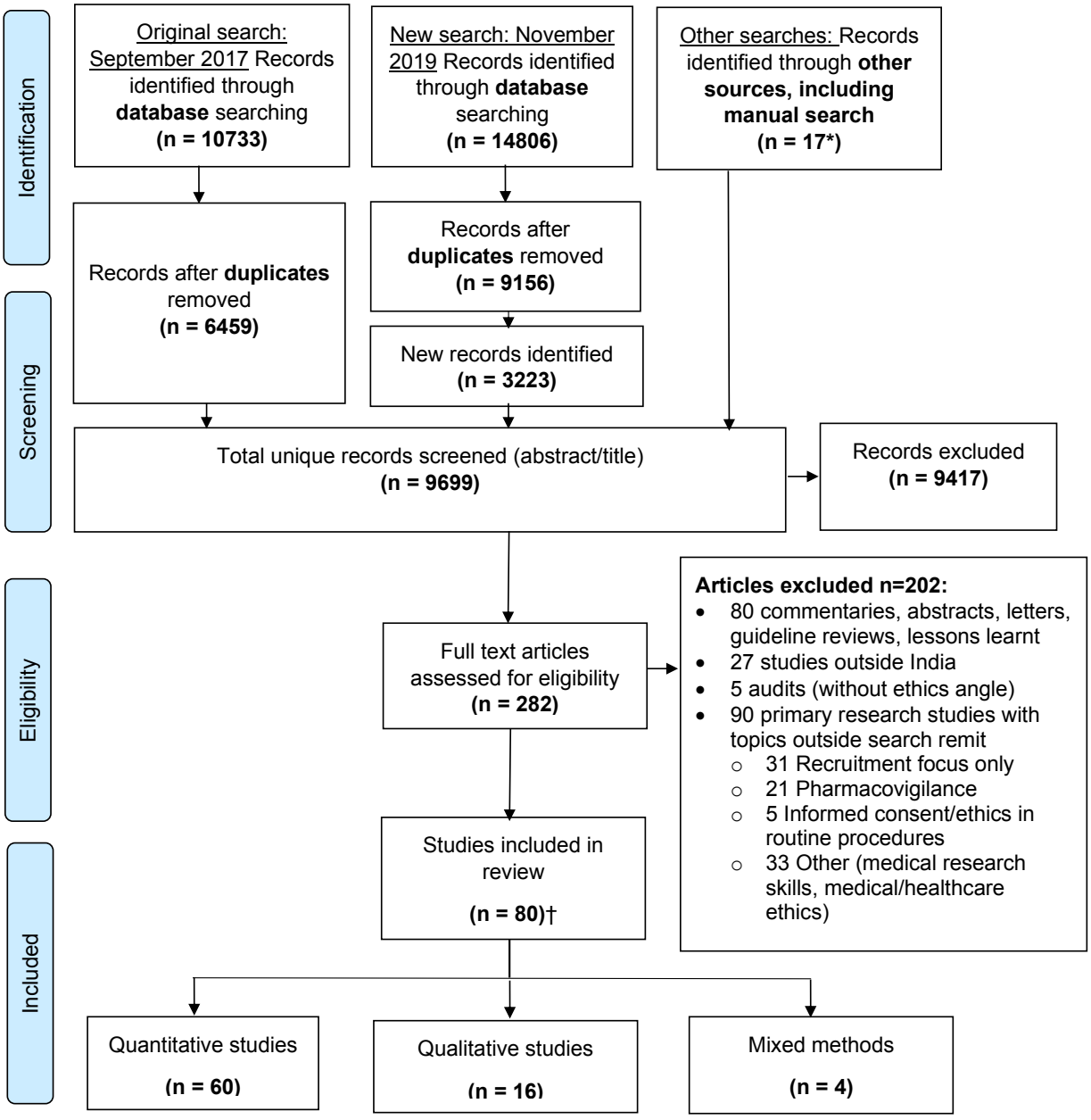

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram.[160] *One study was identified through the consultation exercise. †This includes articles that reported on different aspects of the results derived from the same dataset[73 92 93 107 108] or on different datasets obtained through the same grant.[113 114 120 126 127 160]

research (B1) was synthesised based on the type of documents scrutinised (eg, ethics application forms, informed consent documents, journal articles) and the area under investigation (eg, completeness, errors, quality; reporting practices). The number of articles tagged to a given topic includes studies where that topic was the main focus as well as those where the topic was briefly explored. Salient findings from the synthesis are presented below narratively.

Primary research

The synthesis (table 3) established that, despite the focus on knowledge-based studies evident in the evidence map (table 2), it was difficult to build a coherent picture of lay and professional participants' understanding of the topics explored (written/verbal information provision, clinical trials/research, research ethics, ethics committees), primarily due to the methodological (eg, validity of survey instruments) and reporting limitations in studies

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Table 1 Key characteristics of included studies

Key characteristics (total n=80)	N	%
1. Location		
a. Type		
Urban	**47**	**58.8**
Rural	**3**	**3.8**
Mixed	**3**	**3.8**
Not available*/Not applicable†	**27**	**33.8**
b. Region		
West	**24**	**30**
South	**21**	**26.3**
North	**10**	**12.5**
East	**2**	**2.5**
Mixed (two studies in west and south; two in west, south and north)	**4**	**5**
Pan India‡	**12**	**15**
Not available	**7**	**8.8**
2. Methods		
a. Quantitative	**60**	**75**
Surveys (inferential)	21	
Surveys (descriptive)	15	
Documents (descriptive)	13	
Documents (inferential)	4	
Other (documents, data, observation, RCT, websites)	7	
b. Qualitative	**16**	**20**
Interviews	10	
Interviews and focus groups	3	
Interviews and observations	2	
Interviews, observations, focus groups	1	
c. Mixed methods	**4**	**5**
Survey (descriptive) and interviews	2	
Survey (descriptive) and focus groups	1	
Survey (inferential) and focus groups	1	
3. Population		
a. Professional	**34**	**42.5**
Ethics committee members	8	
Researchers (two with CT investigators; two with clinical research professionals; one with CRO staff)	5	
Healthcare students (five with medical students; one each with nursing and pharmacy students)	7	
Healthcare faculty (two with dental faculty; one with medical faculty)	3	
Healthcare students and faculty (two with dental students and faculty; one with medical students and faculty)	3	
Healthcare service providers (one with healthcare faculty)	3	
Mixed professional groups	5	
b. Lay	**17**	**21.3**
RCT/CT participants (including parents/guardians, healthy volunteers)	6	
Cohort study participants (including parents/guardians)	3	
General public (including those accessed from hospitals)	6	
Specific patient groups (HIV-positive patients; mental health service inpatients)	2	
c. Documents	**22**	**27.5**
d. Mixed (combination of lay, professional, documents)	**7**	**8.8**
4. Journal		
a. Published in India	**49**	**61.3**
b. Published in a high-income country	**29**	**36.3**
c. Unknown/not clear	**2**	**2.5**

*When information is not reported.
†When data collected is documents.
‡Includes surveys, documents, journal articles, websites that were not specific to one region.
CRO, contract research organisation; CT, clinical trial; RCT, randomised controlled trial.

(A1–A4). Methodological research aimed at developing locally validated tools to assess knowledge will help improve the quality of future studies and facilitate meta-analysis.

Ethics committees (A4) were among the most studied topics (18 studies) and also the source of data in a large volume of studies (16 studies, 8 each with committee members and documents submitted to/produced by committees). Studies highlighted a number of challenges faced by ethics committees[73 92 101 102 108 121 130] (eg, conflicts of interest, onerous workload, impact of frequent regulatory changes without support for implementation), which would benefit from the development of interventions to support the optimal functioning of ethics committees. Healthcare students were the next most researched group (10 studies).

Research on interventions to optimise comprehension of written/verbal information provision for informed consent (A1) were particularly lacking (except one RCT that compared group and individual counselling and found no difference in comprehension).[116] While there is some evidence of the difficulties of communicating research terminology (around terms such as research, trial, randomisation) particularly in local languages,[70 112 127] research is required on interventions to overcome these barriers (A2). There was overwhelming support for education and training on clinical trials/research and research ethics in the curriculum for key stakeholder groups, including healthcare students[75 81 98 131 137] but we do not know what, if any, aspects of these topics are currently covered in healthcare students' curriculums so that deficiencies can be identified and addressed (A3).

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Table 2 Evidence map of the number of primary and secondary research articles by topic and population group (studies explored multiple areas and have been categorised by main topic area studied)

			Quantitative			
			Qualitative			
			Mixed methods			
Population ***Topic***			**Lay(a)**	**Professional(b)**	**Mixed(a and b)**	**Total**
A. Primary research: Knowledge (or awareness/comprehension), attitudes (or perceptions), practice (or behaviour)*						
Comprehension of the informed consent form and/or verbal information provision in:						
Real	Randomised Controlled Trial		2[65 116]†			2
	Clinical Trial		3[62 78 82]			3
	Cohort Study		2[87 117]	1[104]		3
Hypothetical	Randomised Controlled Trial		1[80]			1
	Clinical Trial			1[91]		1
Knowledge, Attitudes, Practices in relation to:						
Broad topics:	Clinical Trials		2[122 134]	3[75 100 129]		7
			1[88]	1[112]		
	Clinical Research		2[69 113]	1[131]		3
	Clinical Research Ethics and/or Ethics Committees			5[77 81 98 135 137]		5
Specific topics within:	Clinical Trials	Compensation for clinical trial related injury			1[125]‡	1
	Clinical Research Ethics	Ethical guidelines		1[101]		1
		Informed consent		1[138]		2
				1[114]		
		Ethics committees' composition and/or functioning (incl. ethical review)		3[97 102 130]§		3
Subtotal			**13**	**18**	**1**	**32**
A. Primary research: Perceptions, experiences, practices/processes¶ in relation to:						
Real	Randomised Controlled Trial	Feasibility of informed consent procedure			1[70]	1
		Patient participation in / content of informed consent discussion (examined through audio-visual recordings)	1[83]			1
	Cohort study	Patient participation in informed consent discussion	1[111]			1
	Clinical Trial	Audio-visual recording of informed consent process (description and views)			1[79]	1
	Clinical Research	Recruitment experience/process and informed consent in bioavailability/bioequivalence studies			1[140]	1
Hypothetical	Clinical Trial	Audio-visual recording of informed consent process (acceptability)	1[72]			1
	Clinical Trial and Biobanking Research (meaning of consent, benefit sharing, incentives)		1[127]			1
	Biobanking Research (results sharing, benefits sharing, data ownership)			1[128]		1
Real and hypothetical	Clinical Research	Coercion in research participation		1[126]		1

Continued

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Table 2 Continued

			Quantitative			
			Qualitative			
			Mixed methods			
Population ***Topic***			**Lay(a)**	**Professional(b)**	**Mixed(a and b)**	**Total**
Broad topics:	Clinical Research Ethics and/or Ethics Committees			3[67 133 136]	1[103]	4
Specific topics within:	Clinical Research Ethics	Ethics Committees (composition, functioning, ethical review process)		2[68 108] 2[92 121] 1[73]		5
		Data sharing			1[84]	1
		Outsourcing, Clinical Research Organisations and Civil Society Organisations		3[90 114 115]		3
		Community stakeholder engagement			1[105]	1
		Informed consent documents and processes		1[109]		1
		Impact of regulatory changesf**		2[76 89]		2
Subtotal			**4**	**16**	**6**	**26**
Primary Research Total			**17**	**34**	**7**	**58**

B. Secondary Research

Population **Reviews of:**		**EC documents**		**Informed consent documents**	**Study data / documents**	**Websites**	**Journal articles**	**Total**
		Application forms	**Governance††**					
Completeness, errors, quality		3[85 118 120]			1[110]			4
Payment / compensation for:	Participation	1[99]						2
	Injury			1[64]				
Compliance / adherence with:	Regulations			1[95]				4
	Guidelines		1[123]	1[107]				
	Protocol		1[119]					
Readability				1[86]‡‡				1
Ethics committee:	Registration / accreditation					1[106]		2
	Changes in composition/ structure after regulatory changes		1[66]					
Reasons for uninitiated studies			1[96]					1
Registered clinical trials and disease burden						2[139 141]		2

Continued

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Table 2 Continued

B. Secondary Research

Population Reviews of:		EC documents		Informed consent documents	Study data / documents	Websites	Journal articles	Total
		Application forms	Governance††					
Reporting practices on:	Ethical clearance and/or obtaining informed consent/assent						4[63 71 74 94]	6
	Funding sources and conflicts of interest						1[93]	
	Ethical issues/methods of RCTs; journal editorial policies					1§§[124]		
Secondary Research Total								**22**

Some studies were with parents of children.[83 111 116 117]
Studies where India is one of the countries among others, but where some findings specific to India were reported have been included.[74 93 94 121]
*Studies that explored knowledge/comprehension were included here, even when Attitude and Practice components were not studied; some studies not included here that minimally explored or mentioned knowledge/awareness have been included elsewhere.[66 103 127]
†There is only one RCT[116] in the dataset.
‡This study comprised no lay people, but was categorised as 'Mixed' because the population comprised Professionals and Documents.
§Pharmacovigilance studies were excluded in general; this study was included as it was in relation to clinical trials in particular and included views on EC functioning.
¶Studies that explored perceptions (or attitudes) or experiences or practices, or a combination of these, were included here.
**Five other studies also address the impact of regulatory changes.[66 72 78 79 106]
††Governance related documents included meeting minutes, project registers/files, standard operating procedures, site visit monitoring reports,study approval letters.
‡‡One other study[62] also included readability of informed consent form.
§§Study data included journal articles and website (Clinical Trials Registry-India); could also be categorised within compliance/adherence with guidelines (includes journal editorial policy compliance with international guidelines).
EC, ethics committee; RCT, randomised controlled trial.

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Table 3 Summary of synthesised findings and gaps

Topic	Summary of synthesised findings	Research gaps
A. Primary research: knowledge (or awareness/comprehension) research (with or without attitudes/perceptions and practice/behaviour (or process) components)		
A1. Comprehension of the clinical trial/research informed consent form and/or verbal information provision (within specific studies—real or hypothetical): *lay (and some professional) participants* Number of studies tagged to topic=10	▶ Studies were questionnaire surveys that varied in methodological quality, with most deficiencies being in relation to survey instruments and reporting practices. ▶ Comprehension regarding a large number of aspects were studied among lay participants and reported to be poor on simple (eg, condition under study)[117] as well as advanced concepts (eg, randomisation and blinding).[65 116] Findings were mixed in relation to comprehension of some key concepts such as participant rights—some studies reported participants appeared well aware of their rights,[62 78 82 87] while others noted superficial rather than detailed understanding (eg, being aware of the voluntary nature of participation but not of freedom to decline participation or withdraw without facing adverse consequences).[116 117] Comprehension among professional participants (medical and nursing students) was reported as insufficient.[91 104] Except for one RCT that compared different methods of counselling for informed consent (group and individual; no difference in comprehension found),[116] there were no other interventional studies aimed at identifying strategies that may help improve informed consent. A critical examination of what may constitute optimal understanding or information provision was lacking. The rationale for assessing comprehension was not always clear—only a few mentioned using the outcome to provide further information to participants on topics in which they had a lower score.	▶ (for A1-A4) ▶ Despite a large proportion of studies focusing on knowledge (and attitudes and practices), primarily through questionnaire surveys, it is as yet unclear (a) what aspects of clinical trials/research were often better or poorly understood by lay participants from the informed consent form and verbal information provision, (b) what, if any, aspects of clinical trials/research, research ethics and ethics committees participants (primarily professional) were familiar with. ▶ There is a need for cross-cultural adaptations of questionnaires used in other countries and/or the development of locally validated survey tools to assess knowledge and comprehension. ▶ Research focused on knowledge should also critically examine and report on (a) the purpose of doing this (eg, whether assessing comprehension of informed consent would change local practice) and (b) what constitutes optimal understanding (among research participants) and optimal information provision. Developing a core information set for minimum baseline information to be conveyed to patients is crucial. ▶ There is an immense gap in knowledge regarding interventions that can potentially improve comprehension of research participants in India. ▶ Research is also needed on interventions aimed at: improving communication of research terminology in local languages, evaluating current clinical trials/research and research ethics coverage in healthcare students' curriculum and ways to optimise it, improving knowledge of these topics among healthcare providers and faculty. ▶ Qualitative research studies that chart the actual practice of informed consent rather than the reported practice of it are needed. ▶ Given the existing large volume of studies on ethics committees, research is needed on interventions that support and optimise the functioning of committees to overcome identified barriers.
A2. Knowledge of and attitudes/perceptions to clinical trials/research more generally (not in the context of specific studies): i. *Lay participants* Number of studies tagged to topic=7 ii. *Professional participants* Number of studies tagged to topic=5	▶ Similar to studies above, the methodological limitations of this group of primarily questionnaire surveys hamper a robust understanding of lay and professional participants' knowledge and attitudes to clinical trials/research. ▶ *Knowledge*: the synthesis of findings suggests limited to poor awareness of clinical trials/research among lay[88 113 134 140] and professional participants[75 112 131] (healthcare professionals such as doctors, nurses, counsellors and healthcare faculty and/or students from medicine and pharmacology). There was wide variation in the proportion of lay participants (~25%–60%) who had heard of clinical trials/research[69 113 134] and lack of familiarity with the English term 'clinical trial' among professional participants[112] and the word 'research' or its local translations among lay participants.[127] Lay and professional groups were unfamiliar with the regulations required for biomedical research and/or clinical trials in particular.[75 100 127 129] ▶ *Attitudes*: studies reported generally positive attitudes towards clinical research and its potential benefits across lay and professional groups.[69 75 113 122 127 131 134] Lay participants' concerns revolved around confidentiality, compensation for participation and adverse outcomes, unethical trial conduct and lack of trust in pharmaceutical research.[69 122 127 134] Professional participants had negative attitudes towards pharma or industry-sponsored studies and expressed support for inclusion of clinical trials in the medical curriculum.[75 131]	
A3. Knowledge, attitudes/perceptions and practices in relation to research ethics (including informed consent): *Professional (and some lay) participants* Number of studies tagged to topic=16	▶ As above, these were primarily questionnaire surveys with methodological limitations that limit the synthesis of participants' (mostly professional and some lay) knowledge, attitudes and practices in relation to research ethics and informed consent (eg, many studies did not report if participants had prior clinical trials/research training/experience). Studies were primarily with dental and medical students and/or faculty and professionals from clinical research organisations, and some with ethics committee members, investigators and lay participants. ▶ *Knowledge*: some studies found poor or limited knowledge (self-reported or assessed) of research ethics and ethical guidelines among professional groups,[77 81 137] while others reported good knowledge but poor attitudes and practices in relation to some aspects of informed consent and research ethics[81 98 132 137 138] (eg, some support for fabricating data to improve research outcomes if it did not harm patients and willingness to undertake research rejected by ethics committees). ▶ *Attitudes:* there were generally positive attitudes amongst professional participants towards procedural aspects ofinformed consent[81 98 137] (such as informing patients of risks/benefits and obtaining signatures of participants), but concerns existed amongst lay and professional groups whether the informed consent process and documentation truly protect and inform patients.[67 127] There was overwhelming support for research ethics education for keystakeholders (health students, researchers, ethics committee members),[81 98 137] but no research on what, if anything, was currently covered in the medical/dental curriculum. ▶ *Practice:* there was wide variation in the reported practice of informed consent and some indication of unsatisfactory practices in relation to research ethics and conduct[77 135 138] (eg, in relation to carrying out informed consent in local languages, providing a copy of the consent documentation to patients and maintaining accurate patient records for research). There was indication of coercion among professional participants[126] (medical students) and instances of inadequate informed consent and therapeutic misconception among lay participants.[103] We do not know what information patients expect to be informed about or what recruiters discuss with patients.	
A4. Knowledge, attitudes/perceptions and practices in relation to ethics committees: *Professional (and some lay) participants* Number of studies tagged to topic=18	▶ Ethics committees were among the most researched topics, primarily through questionnaire surveys, with similar methodological limitations as above (eg, missing information on participant demographics and prior training/experience on relevant topics). Studies were conducted with dental and medical professionals (students and/or faculty), ethics committee members, staff from clinical research organisations and lay participants. ▶ *Knowledge*: the synthesis suggests limited knowledge (self-reported and assessed) of ethics committee functioning and composition among medical and dental professionals[81 97 102 135 137] (eg, on quorum requirements, lay representation and frequency of meetings). Lay participants were unaware of role of ethics committees in protecting patient rights.[127] ▶ *Attitudes:* there was widespread support for the existence and need for ethics committees and ethical review amongst dental professionals,[81 98 137] but variation in satisfaction (high[67] to limited[108 135]) regarding ethics committee functioning amongst professional groups (medical and contract research organisation staff). Reported challenges faced by ethics committees (as perceived by contract research organisation staff) included conflicts of interest that compromised their independence and pressures from senior management.[133] The evolution of stricter regulations and guidelines was described favourably by ethics committee members, but they also felt they were too frequentand too many[76 121] with numerous challenges in implementing some of the newer regulatory changes[76] (such as renewal of committee registration). There was overwhelming support for a single national research ethics committee to consider multi-centric trials to prevent 'ethics committee shopping' (where investigators went to different committees until they obtained approval) amongst contract research organisation staff[69 108] but lesser support amongst committee members.[76] Views on how wide the remit of ethics committees should be varied across professional groups (from monitoring serious adverse events to imparting research ethics education to investigators and conducting ongoing monitoring of trials and on-site visits).[68 101 102 108] ▶ *Practice:* research on 'practice' related aspects of ethics committees suggests there were many areas of concern in relation to their functioning and composition[92] (eg, arbitrariness in member selection and lack of choice in refusing membership amongst those affiliated to institutions), responsibilities[92 101 102] (eg, some committees undertook monitoring of ongoing trials and on-site visits, while others did not), workload[73 92 102 108 130] (frequently described as onerous), the ethics review process[73 101 102] (eg, lack of uniformity in documents and ethical aspects reviewed and guidelines followed) and the dilemmas faced in being expected to align with the international standards for ethical review and the increasing pharmaceuticalisation of society, while also protecting national interests and preventing the perpetuation of existing health and social inequities.[121]	

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Table 3 Continued

Topic	Summary of synthesised findings	Research gaps
A. Primary research: perceptions, experiences, practices/processes		
A5. Informed consent processes: *lay (and some professional) participants* Number of studies tagged to topic=13 (of which only 5 were focused on topic)	▶ A small group of studies (n=5) explored the processes involved in informed consent, with a further few (n=8) briefly touching on the topic. Only one study[70] detailed the process of customising the informed consent process to the study population (in an RCT with people with schizophrenia) through feedback from participants/caregivers and then evaluating the process from multiple perspectives. Use of a flip-chart during informed consent and training/ongoing support were found to be useful by participants/study personnel, while research terminology (trial/research, randomisation) was reported as difficult to convey.[70] ▶ *Patient participation in informed consent discussions*: questions asked by parents/guardians of potential child participants (infants) in informed consent discussions varied from 13% to 55% in two studies,[83 111] with education and higher socioeconomic status reported as associated with asking questions.[83 111 127] In healthy volunteer studies, concerns raised by participants revolved mainly around the payment than about their own health. ▶ *Recruitment process/experience and informed consent process*: one study reported on the involvement of paid middlemen to recruit healthy volunteers for bioavailability/bioequivalent studies, serial participation among volunteers and the informed consent process being a mere formality (as decision to participate was often made prior to that). Contrary to views of family involvement in informed consent, healthy volunteers were mostly unaccompanied and had not informed their families of participation due to concerns about being perceived as selling their bodies for money.[140] ▶ *AV recording of informed consent discussions*: acceptability of and support for AV recordings varied (a third of lay participants refused in a hypothetical study and nearly all agreed in a real vaccine trial[72 83]; a third to two-thirds of investigators were in support.[79 89 133] Concerns included the increase in time/resources required to carry out AV recordings and the lack of adequate guidance and support.[79 83 89] Some ethics committees reported reviewing the recordings if there was a need (ie, non-compliance/protocol deviations in the informed consent process).[76] Some investigators believed that the AV recording of the consent process would improve informed consent[83 89 109] (eg, by increasing investigator responsibility), with one study reporting that study participants had better comprehension scores after mandatory AV recording of consent process than before.[78]	▶ (for A5) ▶ Gaps exist in our understanding of (a) models of informed consent that are tailored to the Indian context (ie, community-family based and/or Western-individual autonomy based; in the context of language diversity, illiteracy, health literacy), (b) informed consent/assent in children's clinical research (c) informed consent processes across different contexts (industry or investigator led; student-led trials in medical institutions; healthy volunteer studies and vaccine trials), including recruitment interactions with potential participants and (d) The dual role played by many trial recruiters, where they are also the doctor/healthcare provider and the conflicts of interest and therapeutic misconception arising from same. ▶ Research examining the usefulness of mandatory AV recordings (eg, how often are they accessed for the purpose that they were made mandatory for) and ways in which existing AV recordings can be used to optimise informed consent are needed.
A6. Bigger picture: *professional (and some lay) participants* Number of studies tagged to topic=20 (of which only 7 were focused on topic)	▶ There were a few (n=7), primarily qualitative, studies that explored the larger landscape within which clinical trials were conducted. Four cross-cutting themes were identified, drawing from other studies (n=13). ▶ *Compensation (n=10)*: the synthesis revealed a nuanced discussion among professional and lay participants in relation to compensation for free medicines, for participation and for study-related injuries/serious adverse events. For instance, while lay participants from higher socioeconomic groups felt that the product (vaccine) should be free as it was still being researched, those from lower socioeconomic groups perceived free as inferior or dangerous.[127] Knowledge of and compliance with national laws and guidelines regarding compensation for clinical trial-related injuries varied among investigators, ethics committee members and sponsors (reported as aware to lacking in clarity) and lay participants (reported as completely unaware).[103 125] There was lack of uniformity in how and by whom compensation was determined (eg, by ethics committees, sponsor or investigators) and for what purposes (eg, lost wages, travel, participation, injuries or their management),[76 103 125] with some evidence of healthy volunteers being able to bargain for incentives higher than what was approved by ethics committees.[140] ▶ *Sharing of data, blood/tissue samples, results and benefits (n=3)*: the limited experience of participants (lay and professional) in relation to data sharing amplified their concerns about it.[84] Despite the small number of studies on the topic, issues were well explored in relation to what is data,[84] views on sharing of blood/tissue/medical records (lay participants often readily agreed at the start but were more discerning when given further information),[127] different types of consent for data sharing[84 127] (eg, blanket/broad, middle or explicit consent), disclosing individual findings following the use of biobanking research[128] (eg, there was some support for disclosing actionable individual results, while recognising the challenges to the process and contrasts with high-income countries where individual results are usually not shared), sample ownership in biobanking research[128] (eg, patients', custodians' or researchers') and benefit sharing[127 128] (eg, giving back to the community, especially when outcomes of studies are commercialised for profits). ▶ *Power imbalances (n=17)*: unequal power dynamics were explored across different groups and contexts. These ranged from local issues such as lay members of ethics committees feeling stifled by medics and scientists[92 133] and paternalistic doctor-patient relationships contributing to therapeutic misconception about clinical trials,[127] to larger issues such as the lack of correlation between India's disease burden and its clinical trials,[90 92] capacity building being more about implementation of agendas set by international pharma companies and procedural efficiency than the nurturing of local innovation and leadership,[114 115] the exploitation of disadvantaged groups in clinical research[103 105 114 140] (eg, targeting of recruitment within poor, rural, tribal and unemployed groups), paid healthy volunteers being exploited due to their lower socioeconomic status while also being able to bargain for higher incentives than approved by ethics committees (many viewed trial participation as an alternative career)[140] and ethical variability and the continuation of a neo-colonialist relationship between the West and India.[109 112 113 121] The larger issues were highlighted by members of civil society organisations and ethics committee members, but less so by those from the private sector and contract research organisations, who argued against ethical variability across the West and India and felt that clinical trials were relevant to the needs of India.[67 90] Patient and public involvement was under-researched, except for one study on community engagement.[89] ▶ *CROs, CSOs and the clinical trial industry (n=7)*: some studies provided a detailed account of the growth of CROs in India (with 'big-pharmaceuticalisation' used to describe Indian pharma companies' move from generic drug manufacturing to innovative research), CRO operations and processes employed for recruitment (in the context of healthy volunteers)[140] and the vital role played by CSOs in changing the regulatory landscape in India[114 115] (few other studies also explored related topics[140]). CRO staff were critical of reports of malpractice, but saw these as issues within other rather than their own CROs (although there was evidence to the contrary).[115 140] There was some distrust of pharma-sponsored trials among doctors, ethics committee members and CSO staff,[75 92 114] while investigators from the private sector (in a study authored by researchers from a pharma company) expressed favourable views regarding pharma-sponsored trials.[67] CSO members were supportive of RCTs, but lamented the lack of focus on wider ethical issues that went beyond procedural and informed consent focused agendas. Their accounts drew from interpretations of a social justice-based approach to health, while also highlighting an evolution of their views from the purely ideological to the more pragmatic (a move away from dichotomies such as Indian/public-good and foreign/private-bad).[114]	▶ (for A6) ▶ Although few in number, existing studies provide rich insights on the Indian clinical trials landscape. ▶ Research on real compensation awards, especially for study-related injuries, would help chart out current practice, so that recurrent areas of concern can be addressed. The challenges with the implementation of compensation rules could be explored in future studies, especially in light of the recent NDCT Rules, 2019. ▶ Empirical information on participant profiles across a range of clinical trials will help inform debates around the recruitment of vulnerable groups. ▶ Similarly, qualitative research on doctor (or recruiter)-patient interactions would provide empirical evidence on aspects of communication that contribute to or strengthen therapeutic misconception in trial recruitment (so that interventions can be developed to optimise communication). ▶ The impact of the NDCT 2019 Rules in redressing concerns such as conflicts of interest and power imbalances within ethics committees would need to be examined. ▶ Further research, especially qualitative, to expand the scope of discussion on issues of equity and justice in clinical trials in India and the role of social determinants such as gender, poverty, caste and their intersectionality would add to the existing rich but small number of studies on the topic. ▶ There is an immense gap in relation to research on patient and public involvement in clinical trials.

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Table 3 Continued

Topic	Summary of synthesised findings	Research gaps
B. Secondary research		
B1. Documentary reviews Number of studies tagged to topic=23	▶ Documents, primarily sourced from ethics committees (such as informed consent documentation, application forms, meeting minutes, site visits, approval letters) were examined for quality, coverage of issues such as compensation and compliance with legal frameworks and good clinical practice guidelines. Documentary research highlighted inadequate informed consent documentation,[119] increased workload for ethics committees after the regulatory changes of 2013,[66] inequities in the distribution of clinical trials, medical colleges and ethics committees across different states in India (reflecting existing health inequalities),[106] mismatch between India's disease burden and areas researched in clinical trials,[139 141] evidence of 'ethics shopping' (multicentric studies that had not resolved queries raised by one ethics committee were found to have gained approval at another committee),[96] inadequate mention of compensation arrangements in ethics committee application forms and informed consent documents[64 99 107 120 125] (with some indication of improvements over time). Where readability of informed consent forms was examined, it was through Western readability tests.[86 107] ▶ A small group of studies also looked at reporting practices in journals from India, mostly in relation to ethical approval and informed consent, and found that this information was often missing or suboptimal.[63 71 74 94] Methodological and ethical issues were found to be better reported in the clinical trials registry in India than in journals.[124]	▶ (for B1) ▶ Empirical evaluations of the regulatory processes, including number of trial applications submitted for approval per year, numbers approved and disapproved and reasons for the same, will help researchers better understand how regulations are applied to trial applications. ▶ Research to develop readability tests in Indian languages may help in improving informed consent forms, which could also be examined for issues beyond compliance with legal frameworks/guidelines (such as whether trial treatments are presented in a balanced manner). ▶ Studies on reporting practices of surveys published in Indian journals would help highlight the key methodological issues that can be improved.

AV, audio-visual; CRO, contract research organisations; CSO, civil society organisations; RCT, randomised conrolled trial.

There is some evidence in relation to the 'reported' practice of informed consent[77 126 135 138] (eg, not conducting informed consent in local languages or indication of coercion among student research participants), but limited[70 83 111 140] information on the 'actual' practice of gaining informed consent, what research participants consider important to know or models of informed consent that are tailored to the local context (A3, A5). Where 'actual' practice was examined, it was illuminating—for instance, in healthy volunteer studies, informed consent appeared to be a formality and discussions were centred around payment for participation than risks to volunteers' health.[140] Future research on informed consent processes should include an in-depth exploration of the recruitment interaction with potential research participants that delves beyond the questions participants ask, towards the identification and dissemination of good practice, across multiple contexts (eg, consent/assent in trials with children; student-led trials in academic institutions). A good starting point would be to explore if it is feasible, within the current regulatory framework and following strict confidentiality requirements, to use the AV recordings of the consent process more proactively for these purposes, rather than be reviewed only when there are reports of ethical misconduct.[76] Similarly, the development of core information sets that help define the essential information that participants would like to receive is warranted (A3, A5).

The small group of studies (A6; seven studies) that focused beyond the surface issues around clinical trials provided rich insights into the origins, growth and workings of the clinical trials industry, while placing the industry within the wider regulatory environment and existing health inequities. Four key cross-cutting themes were examined among these primarily qualitative studies (informed by other qualitative/quantitative studies that touched on similar areas):

i. Compensation (for study participation, treatment or study-related injuries) was well researched and studies highlighted the need for a nuanced consideration of compensation arrangements[127] (to account for views such as free treatment being perceived as inferior/dangerous by those from lower socioeconomic groups). It also appeared that compensation determination is fraught with challenges[76 103 125 140] (such as lack of uniformity in the process and incentives approved by ethics committees being overridden). Studying current practice in relation to actual compensations that have been awarded may help chart out areas of inconsistencies that can be addressed. Also, there appear to be challenges with implementing and complying with the compensation rules, which could be investigated in future studies (no studies were conducted after NDCT Rules 2019).

ii. Data sharing was explored in a small volume of studies[84 127 128] that nonetheless provide valuable insights. For instance, lay participants appeared cautious about consent for data sharing after receiving detailed information (despite readily agreeing initially)[127] and some professional participants supported sharing clinically relevant and actionable results with individuals who contributed to biobanking research, but acknowledged the challenges to this process.[128]

iii. Power imbalances within the clinical trials/research environment were frequently discussed by professional participants, especially members of ethics committees and civil society organisations. Imbalances of concern included the paternalistic doctor-patient relationship contributing to therapeutic misconception[127] (where participants perceive unproven trial treatments to be beneficial), the lack of correlation between India's disease burden and diseases studied,[90 92] the equation between paid healthy volunteers (exploited due to their lower socioeconomic status) and contract research organisations (with whom the volunteers have bargaining power),[140] capacity building that does not foster local innovation[114 115] and the hierarchy between medical and non-medical experts in ethics committees.[92 108 133] Some of these concerns would benefit from empirical investigation—for instance, studying the doctor-patient interaction in trial recruitment can help delineate the components of

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communication that contribute to therapeutic misconception. Similarly, research, particularly qualitative, that further explores issues of equity and justice in relation to clinical trial recruitment processes is warranted. Research on patient and public involvement in clinical trials is conspicuous by its absence and should be prioritised to redress some of the power inequities.

iv. A small group of studies provided nuanced insights into organisations that appear to be at opposite ends of the ethical debates on clinical trials in India—contract research organisations (CROs) and civil society organisations (CSOs).[114 115] Although critical of ethical malpractice in general, CRO staff were less inclined to acknowledge instances of the same in their own CROs.[115] CSO representatatives were supportive of clinical trials, felt the need to move away from pitting Indian and/or public sector clinical trials against foreign and/or private sector clinical trials as good versus bad and emphasised the need to focus on wider ethical issues that delve beyond simplistic procedure-based agendas.

Secondary research

The synthesis of documentary research (B1) corroborated findings from the synthesis of primary research and reported: inadequacies in informed consent documentation, increased workload for ethics committees particularly after the 2013 regulatory changes, mismatch between clinical trials and India's disease burden, lack of uniformity in compensation mechanisms and suboptimal clinical trial reporting practices in Indian journals.[64 66 71 74 119 124 125 139 141] The use of Western readability tests for written information provided in India[62 86] needs addressing with the development of readability tests in Indian languages. Similarly, while studies on journal reporting practices have focused on the reporting of ethical approval and informed consent, future studies could investigate reporting practices in relation to questionnaire surveys (given their frequent use and methodological/reporting limitations as indicated earlier).

Consultation exercise

Nine of the 10 individuals approached agreed to participate in the consultation exercise (virtual conferencing group: n=7, one meeting, 1 hour 30 min; telephone: n=1; email: n=1). The consultation group's recommendations and actions taken were grouped into five key areas as summarised in table 4 (detailed in online supplemental file 5).

DISCUSSION

We carried out a scoping review and narrative synthesis of the empirical literature on ethical issues in relation to clinical trials/research in India. We developed an evidence map of 80 studies and synthesised the findings narratively, revealing a wide range of topics investigated and the gaps that exist, with key insights from the consultation group. We found that some topics and populations were more favoured than others—the literature was heavily focused on 'knowledge' assessments of participants from lay/professional groups on various topics; ethics committees were examined from multiple angles while also being the source of data in many studies and healthcare students were often research participants. On the other hand, studies that investigated the recruitment-informed consent process, models of informed consent tailored to the Indian context and issues such as equity and justice in the context of clinical trials/research were far fewer in number or absent.

To our knowledge, this is the first systematic scoping review that focuses on empirical research on the ethical aspects of clinical trials/research in one country. Systematic reviews on related aspects (eg, willingness to participate) have tended to combine LMICs together[44] or included people living in India with those of Indian origin living in other countries.[45]

Our findings indicated that the volume of literature on a given topic was not associated with whether or not it allowed the development of a cohesive synthesis on the topic. We found it challenging to develop a lucid picture of some frequently researched areas such as knowledge on clinical trials/research and research ethics. Given the diversity and scale of the population in India, this could be a reflection of reality, but the numerous methodological limitations and reporting variations, particularly among questionnaire surveys, made it difficult to identify commonalities that may exist. By contrast, although only a small number of studies focused on the wider ethical issues, they provided valuable insights into the workings of the clinical trials/research industry. This may also be because the former group of studies, primarily questionnaire surveys, were likely aiming for breadth but were often compromised methodologically, while the explorations of wider ethical issues were more amenable to qualitative research and successfully provided the depth that was warranted in intense and nuanced debates.

Research gaps were identified on topics that need to be researched (when limited or missing from current literature) as well as topics that need to be 'better' researched (when present in literature but requiring methodological/reporting improvements). Given that questionnaire surveys (particularly those exploring knowledge) were the predominant method used, methodological research on developing and validating culturally relevant survey tools and minimum journal reporting standards for surveys would be crucial, drawing from existing guidelines.[144–146] Small-scale, single-centre surveys may be useful to inform local practice, but consistent use of validated measures and standardised reporting practices are needed to contribute to national policy and practice. Calls to ensure inclusion of research ethics and clinical trials education in the curriculum of healthcare students would be bolstered if research can establish and evaluate the content of aspects that are already covered.

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Table 4 Recommendations from the consultation group and actions taken

Area	Recommendations	Action
1. Improving the manuscript	► Change title to better reflect the scope of the review. ► Ensure better acknowledgement of the rich bioethics literature and lack of grey literature in the review. ► Incorporate a reflexive section on the authors. ► Emphasise the value of qualitative research in addressing key research gaps.	Reflexive note in online supplemental file 5; others incorporated in manuscript.
2. Additional analysis and missed literature	► Consider impact of the 2013 regulatory changes. ► Consider impact of studies' funder/sponsor on the research landscape. ► Examine four missed articles for inclusion.	► Additional analysis undertaken (data extracted for year of data collection and funder). ► One article met inclusion criteria and was included; others, where relevant, have been mentioned in methods/discussion.
3. Research gaps	There is insufficient empirical information on: ► Informed consent/assent processes for children in clinical trials/research. ► Models of informed consent to suit multiple contexts. ► Issues of equity and social justice in relation to clinical trials. ► Doctor-recruiter dual role and the arising conflicts of interest. ► Regulatory processes. ► Academic trials conducted in medical institutions and vaccine trials. ► Therapeutic misconception. ► Questionnaire validation processes.	These gaps have either been highlighted separately within the review or incorporated within existing gaps.
4. Reasons for paucity of research	► Lack of funding initiatives to carry out nested studies within clinical trials and related methodological work is a major obstacle for researchers in India. ► Not all ethical issues are 'researchable' and are sometimes better captured through bioethics literature.	Incorporated in discussion.
5. Concerns	Most concerns expressed were in relation to ethics committees: ► Lack of awareness of principles underpinning clinical research and good clinical practice guidelines among committee members. ► Non-trial study designs encouraged by committees to avoid institutional liability for serious adverse events in clinical trials. ► Excessive workloads and undeclared roles and conflicts of interests among members.	Noted here as this is a reflection of the large proportion of studies on ethics committees.

The direct impact of the 2013 regulatory changes on the research landscape are unclear in this review. A few studies investigated professionals' perceptions of regulatory changes,[76 89] acceptability and impact of new measures such as the AV recording of consent[72 78 79] and the impact of changes on ethics committees[66 106] (latter is examined in-depth in an excluded literature review[147]). It would have been useful to further examine the review findings through the prism of the landmark 2013 regulatory changes, but with a third of the studies not reporting the year of data collection, this was not feasible. It is also important to interpret the findings in light of the continually evolving regulatory landscape in India, with the most recent changes introduced in March 2019 (NDCT Rules).[19] For instance, some studies raised concerns in relation to the conflicts of interest that compromise the independence of ethics committee members and the hierarchy between medical and non-medical (lay) members of ethics committees, stemming partly from issues such as lack of adequate training for lay members.[92 108 133] With the NDCT Rules now requiring 50% of members to not be affiliated to the institution in which the committee is based and necessitating mandatory training for ethics committee members,[148] future studies can investigate if this has redressed some of the concerns around the independence of ethics committees and the power imbalances within. Similarly, Indian regulations on compensation for trial-related injuries are acknowledged as comprehensive and having unique features (eg, the compensation for injuries not related to research),[149] but it would be crucial to study the challenges in the implementation of these national laws on compensation.

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The views expressed by some participants (and authors) of studies in this review that there was an excessive focus on the proceduralism of informed consent is conceivably true in practice and appears well documented,[67 90 101 121] yet the informed consent process was grossly under-researched. Given the breaches of good practice reported in the past and the routine AV recording of the informed consent interaction, it is notable that only one study[83] was conducted using this resource. It is unclear if the challenges in undertaking, storing and retrieving AV recordings[150 151] has a role in their underutilisation for research purposes or if this is due to regulatory restrictions. Opening the black box of the informed consent process in future qualitative research can help optimise comprehension of participants, communication of complex trial-related terminology in local languages and identify aspects of the doctor-patient interaction that contribute towards therapeutic misconception.

Given the lack of established benchmarks for what constitutes optimal information provision for potential clinical trial participants in India or in the West,[152] researchers could also establish core information sets (information of core importance to convey to patients, drawing from empirical evidence and consensus building approaches.[153] Patient and public involvement would need to be a central component in such efforts. Interventions to identify informed consent models that are suited to the Indian context (community-family based and/or Western-individual autonomy based) and to specific situations (eg, industry-led and investigator-led trials) are warranted.

It would also be useful to critically consider the topics, populations and methods that we, as researchers, choose to investigate and employ in future studies—for instance, (a) whether the ease of access to healthcare students and ethics committee members and/or its documentation justifies them being frequently researched, especially when they are so unrepresentative of participants in trials or (b) whether assessing comprehension of informed consent information is meaningful without assessing the quality of written and/or verbal information provision that preceeded it. Future research could also address the lack of readability tests in Indian languages, develop interventions to improve ethics committee functioning by overcoming some of the identified barriers and curtail the excessive focus on 'knowledge' to redirect efforts on the larger ethical issues to tackle the inequities and imbalances in the clinical trial industry.[90 92 105 112 114 115 121 127 128] However, if knowledge assessments were to be undertaken, it would be prudent to consider what constitutes optimal understanding among research participants[152] and whether the outcome of any knowledge assessments can be used to improve the informed consent process or the comprehension of participants locally. The suitability of interventions employed in high-income countries to improve participant understanding in informed consent for research[154 155] needs to be carefully assessed for India. Qualitative research methods, underused in the range of topics covered in this review, are best suited to investigate the larger issues that require depth of understanding rather than breadth.

The consultation exercise with key stakeholders in India was instrumental in contextualising this scoping review and identifying missed research priorities. A key structural constraint identified in the consultation exercise and evident in the dataset was that most studies were conducted with no to limited external funding. Calling for high-quality studies that span a range of topics to fill the identified gaps would be misguided without appropriate funding mechanisms. Initiatives such as the Medical Research Council's trials methodology hubs across the UK have been instrumental in improving clinical trial design, conduct and reporting (eg, see final report of trials methodology research carried out over 4 years, 2014–2018, in one of the hubs[156]), with subsequent provisions for initiating trials methodology projects in LMICs.[157] It is time for international/national funding agencies to consider establishing similar methodology hubs led by researchers in India, with a focus on the ethical conduct of clinical trials. It would be important, however, to ensure that in our pursuit of empirical evidence, we do not downplay the vital role played by other forms of evidence and catalysts for change, given that not all ethical issues are amenable to being researched.

Limitations

Despite our best efforts, we may have missed some relevant journal articles and studies included in books. However, if missed articles reflected the patterns of published research included in this review, it is likely that they would not substantially alter our synthesis and conclusions. A decision to only include peer-reviewed research also meant we did not seek out grey/unpublished literature[158 159] (although condensed publications from them, if any, are included[103]). Some of the topics we excluded may have helped contexualise our findings. For instance, we included studies on research ethics but excluded those on medical/clinical ethics—an associated topic of interest that requires a separate review.

While the review has helped underline the gaps in the existing literature, it is not exhaustive and cannot claim to have identified all gaps. It also cannot prioritise the identified gaps in a meaningful way and is limited in identifying key topics that are completely absent or of importance to key stakeholders. Designing and conducting the review with the input of researchers in India from conception stages may have resulted in a different focus and outcome. Our intention was that the critical input of key stakeholders at the consultation phase helped focus the review and overcome some of the shortcomings. A locally led priority-setting exercise, informed by this review, to determine pressing concerns that warrant empirical investigation would be an ideal next step.

CONCLUSION

This systematic scoping review is the first attempt at summarising peer-reviewed empirical research on topics related to the ethics of clinical trials/research in India.

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The review demonstrates that while a wide range of topics have been studied in India, the focus is largely on assessing knowledge levels across different population groups. This is a useful starting point, but fundamental questions remain unanswered about the recruitment and informed consent process, such as the doctor-patient interaction, and the larger issues of equity and justice that dominate the clinical trials/research landscape.

The evidence map and narrative synthesis are meant to be a starting point for discussions on future research directions, to be used in ways that benefit the research community and patient population and contribute towards the ongoing efforts within India to improve the clinical trials/research ecosystem. A priority-setting exercise that could be informed by this review, led by researchers in India, would be an ideal next step, alongside funding mechanisms that support researchers based in India to undertake research in priority areas in clinical trials/research methodology and ethics.

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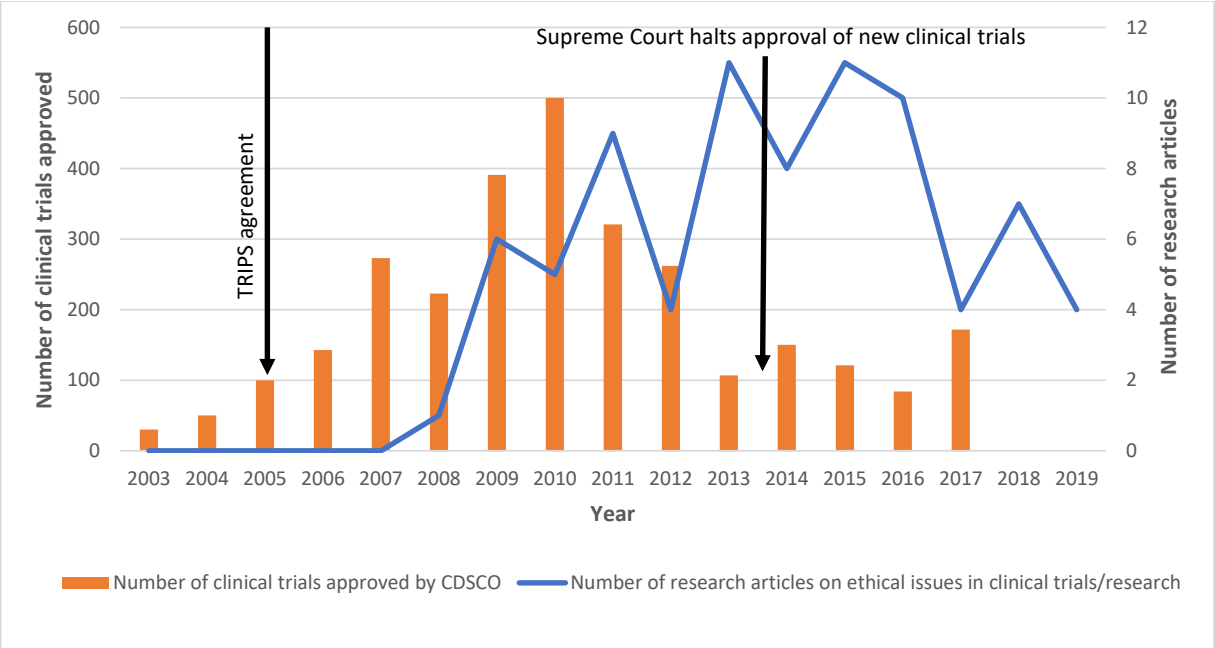
Supplementary file 1: Figure - Clinical trials approved in India by year and the evolution of research on the ethics of clinical trials in India mapped against key regulatory developments



Source: Data on number of trials approved by CDSCO (Central Drugs Standard Control Organisation) is taken from multiple articles; 2003-2008;[2] 2009-2014;[3] 2015-2017[31]

Supplementary file 2: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Introduction, para 1-3; Methods, para 2
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Methods, para 3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Methods, para 2
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Methods, para 4-6
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Methods, para 6
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplement 4
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Methods, para 7
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, para 8-9
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Methods, para 8
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Methods, para 9

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Methods, para 10
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Results para 1-4; Table 1; Supplement 6
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Summarised within narrative synthesis – Table 3 and Supplement 7
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Table 2; Supplement 6
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Results para 5 to end; Tables 2 and 3; Supplement 7
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Discussion, para 1-9
Limitations	20	Discuss the limitations of the scoping review process.	Limitations, para 1-2
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Conclusion, para 1-2
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	For included sources of evidence: Results para 4. For scoping review: Funding section of manuscript.

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Supplementary file 3: Inclusion criteria for identification of eligible studies

Setting	India (other South Asian countries included in search, but not in any further steps reported)
Population	Any stakeholder groups • Lay – patients/patients' guardians, public, CT/cohort study participants; • Professional – healthcare/research faculty, students or practitioners, members/staff of ethics committees or regulatory/governmental agencies • Other – relevant documents
Phenomenon of interest	Any ethical aspects of conducting clinical trials/research in India (e.g. informed consent, scientific misconduct, research governance, ethics committees and approvals, good clinical practice)
Study design	Primary/secondary research of any design conducted on human participants (including observational, experimental, quasi-experimental, randomised controlled trials, qualitative, mixed methods)

Supplementary file 4: Medline search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp Informed Consent/ (39822)
2 consent*.tw. (66248)
3 (informed adj2 (decision* or choice*)).tw. (9675)
4 exp Comprehension/ (11748)
5 exp Awareness/ (18083)
6 exp bioethical issues/ or exp bioethics/ or exp complicity/ or exp "conflict of interest"/ or exp ethics committees/ or exp ethics, institutional/ or exp ethics, professional/ or exp ethics, research/ or exp professional misconduct/ (106864)
7 scientific misconduct.tw. (863)
8 therapeutic misconception.tw. (216)
9 exp Disclosure/es, lj [Ethics, Legislation & Jurisprudence] (4428)
10 disclos*.tw. (70367)
11 research governance.tw. (246)
12 good clinical practice.tw. (1424)
13 exp Confidentiality/ (50771)
14 *Health Knowledge, Attitudes, Practice/ or *patient education as topic/ (86839)
15 ((understand* or knowledge or perception* or comprehend* or comprehension or awareness) adj12 (barrier* or research or study or studies or trial or trials)).tw. (292135)
16 (information adj3 (patient* or volunteer* or participant* or recruit or recruits) adj3 (study or studies or research or trial or trials)).tw. (1179)
17 or/1-16 (661221)
18 exp Clinical Trial/ (831342)
19 exp Clinical Trials as Topic/ (322063)
20 exp drug approval/ or exp drug evaluation/ or exp feasibility studies/ or exp pilot projects/ (217419)
21 exp Human Experimentation/ (12631)
22 exp Research Subjects/ (15759)
23 ((participa* or tak* part or enrol* or volunteer* or recruit* or subject*) adj7 (trial or trials or research or study or studies)).tw. (552279)
24 ((patient* or candidate*) adj7 (trial or trials or research or study or studies) adj7 (choose* or chosen or choice* or select*)).tw. (20782)
25 (exp Patient Participation/ or *patient selection/ or *volunteers/ or *health personnel/ or *research personnel/) and (trial or trials or study or studies or research).tw. (32320)
26 researcher subject relations/ (1086)
27 *drug industry/ (19424)
28 or/18-27 (1709573)
29 exp bangladesh/ or exp bhutan/ or exp india/ or exp nepal/ or exp pakistan/ or exp sri lanka/ (126661)
30 (bangladesh or bhutan or india or nepal or pakistan or sri lanka).tw. (112390)
31 exp Developing Countries/ (71257)
32 exp Contract Services/ (12492)
33 outsour*.tw. (1525)
34 contract research organi#ation.tw. (76)
35 or/29-34 (243873)
36 17 and 28 and 35 (3178)
37 letter/ (992989)
38 editorial/ (452191)
39 news/ (186037)
40 exp historical article/ (387093)
41 Anecdotes as topic/ (4934)
42 comment/ (705965)
43 (letter or comment*).ti. (127313)

44 or/37-43 (2228855)
45 36 not 44 (2827)
46 exp animals/ not humans/ (4581034)
47 exp Animals, Laboratory/ (836666)
48 exp Animal Experimentation/ (8778)
49 exp Models, Animal/ (516385)
50 exp rodentia/ (3100283)
51 (rat or rats or mouse or mice or rodent*).ti. (1315778)
52 or/46-51 (5412057)
53 45 not 52 (2811)

Supplementary file 5

A. Members of the consultation group

Names (in alphabetical order)	Role and Organisation	Method of consultation
1. Dr Amar Jesani	Co-founder of the Forum for Medical Ethics Society; Editor Indian Journal of Medical Ethics; Faculty member, Centre for Ethics, Yenepoya University, Mangalore, India	Virtual group meeting*
2. Dr Anant Bhan	Researcher in Global health and bioethics; Adjunct Professor, Centre for Ethics, Yenepoya University, Mangalore, India; Former President, International Association of Bioethics; Lead, Sangath-Bhopal, India	Virtual group meeting
3. Professor Gagandeep Kang	Professor of Microbiology, Wellcome Trust Research Laboratory, Division of Gastrointestinal Sciences, Christian Medical College, Vellore, India	Virtual group meeting
4. Dr Manjulika Vaz	Lecturer, Health and Humanities, St. John's Medical College, Bangalore, India	Virtual group meeting
5. Professor Nithya Gogtay	Professor and Head, Department of Clinical Pharmacology, Seth GS Medical College and King Edward Memorial Hospital, Mumbai, India	Telephone
6. Dr Rashmi Rodrigues	Associate Professor, Department of Community Health, St. John's Medical College, Bangalore, India	Virtual group meeting
7. Ms Sarojini Nadimpally	Executive Director, SAMA Resource group for women and health, New Delhi, India	Virtual group meeting
8. Professor Urmila Thatte	Emeritus Professor, Department of Clinical Pharmacology, Seth GS Medical College and King Edward Memorial Hospital, Mumbai, India	Virtual group meeting
9. Dr Vijay Gopichandran	Assistant Professor, Community Medicine, ESIC Medical College, Chennai, India	Email

***** The virtual group meeting was held on October 23rd, 2020

B. Reflexive note on the systematic scoping review's authors: The authors of this paper are qualitative researchers (SP, JW, LR, NM, ARe, JD), systematic reviewers (PD, AR), bioethicists (JI, RH, SS) and clinician-researchers (JR, JB). SP was born, raised and educated first in India and then in the UK, with brief clinical work experience in India and research experience primarily in the UK. JR and SS have carried out research in India. All other authors primarily conduct research in the UK.

Amongst the authors, SP, JI, JR and JD and amongst the consultation group, AJ, AB, NG, SN and UT are involved in a recently-funded feasibility study (MRC-NIHR Trials Methodology Research Partnership global health pump-priming grant) on optimising informed consent in clinical trials in India, as co-applicants, collaborators or advisory panel members.

C. Summary of key recommendations from the consultation exercise

	Recommendations, explanations and current concerns raised by the consultation group and the actions taken thereof in the manuscript
1. Improving the manuscript	• Title: Previous title ('Ethical issues in clinical trials in India: a systematic scoping review and narrative synthesis to map the quantitative and qualitative evidence and identify research priorities') was considered problematic as it suggested that the review was identifying ethical issues in clinical trials in India, which was not the aim of the authors. Also, the review was broad and included 'clinical research and clinical trials' but the title only mentioned 'clinical trials'. ***Action:*** *Title was changed to 'What empirical research has been undertaken on the ethics of clinical research in India? A systematic scoping review and narrative synthesis to map the evidence.'*

	• Bioethics literature: Ensure better acknowledgement of the bioethics literature that includes reflective, narrative and philosophical debates, as well as case studies of ethical misconduct, which have not been covered in this scoping review, but have been instrumental in changing the regulatory landscape in India. ***Action:*** *Acknowledged in the introduction.* • Grey literature: Acknowledge limitations of not including grey literature, including studies that may have been reported in books. ***Action:*** *Mentioned in the limitations.* • Reflexivity: Include a note on reflexivity to ensure lead author's views regarding own background as expressed at the meeting are presented to the readers. ***Action:*** *Included above in this supplement.* • Qualitative research: The role of qualitative research in providing rich empirical evidence to address some of the gaps needs to be strengthened in the manuscript. ***Action:*** *Further emphasised in the discussion.*
2. Additional analysis to undertake for this scoping review and published or unpublished literature to consider	Analysis: • Impact of 2013 regulatory changes: Consider the impact of the regulatory changes in relation to ethics committees (i.e. to examine if the regulatory changes made a difference to how committees operated before and after 2013) and if there are any significant changes in the nature/type of studies in the scoping review dataset or in the findings more generally before and after 2013. ***Action:*** *To facilitate this, additional analysis undertaken involved extracting the year of data collection from studies, but this demonstrated that a large proportion of studies did not report the year of data collection; this has now been included in the results and limitations sections. A review paper (excluded from this scoping review) that describes the impact of the 2013 regulatory changes on ethics committees in detail[147] has been included in the discussion section of this scoping review.* • Study funder/sponsor: Consider whether it is possible to examine the studies based on who funded/sponsored the study, as the type of studies conducted or the issues explored may vary based on whether sponsored by academic centres or not. ***Action:*** *Additional analyses involved extracting and analysing each paper's corresponding author's institution (academic or not), declarations of source of funding and conflicts of interest – included in the results and discussion sections.* Literature • Published research: a. A qualitative study on ethical issues in the recruitment of healthy volunteers was highlighted as missing from the scoping review. ***Action:*** *This has now been included in the manuscript results.[140]* *b.* Some studies that report on the Clinical Trials Registry India data were highlighted during the consultation exercise. These provide valuable information but audits of the Clinical Trials Registry of India were excluded where they reported the number of trials registered per year[40] or highlighted the deficiencies in the data[41] (and included if they were linked to an ethical issue[139,141]). ***Action:*** *This has now been further clarified in the methods.* • Grey literature: Two studies undertaken by SAMA, New Delhi were mentioned during the consultation exercise and later sent to the scoping review lead (an unpublished comparative study examining compensation mechanisms in seven countries including India[158] and a full unpublished report[159] of a published and included study.[103] ***Action:*** *These have been mentioned in the limitations section.*
3. Research gaps	• Children in RCTs: There is a notion that parents would be less inclined to allow their children to participate, yet experience on the ground suggests that parents are willing to allow their children to participate. Research questions to consider: What drives parents to allow children to participate in trials? What are the issues in the consenting process? How is assent taken care of? ***Action:*** *Informed consent/assent in relation to children's participation in clinical research has been included as a research gap.* • Informed consent:

	○ It is unclear how written consent is operationalised in a country like India where a large proportion of the population is illiterate or not literate in the language of the consent form. Research questions to consider: How is written consent obtained in the context of multiple languages, illiteracy and healthy literacy in India? Does picture-based informed consent work better than video consent? ***Action:*** *Expanded section on models of informed consent in gaps identified.* ○ There is a need to develop models of informed consent that are based on communitarian models suited to the Indian context rather than the Western libertarian/autonomy models that currently inform our regulations/guidelines. ***Action:*** *This has been further emphasised in the review.* • Recruitment process: There is a need to develop a sound empirical holistic understanding of the entire continuum of the recruitment process, that takes into account issues of equity and fairness as well as social determinants such as gender, poverty, caste and class and their intersectionality. Most of the clinical trial recruitment happens from the hospitals where the health care providers are themselves the researchers; there exists a strong conflict of interest, which needs to be explored. ***Action:*** *Further emphasised in the review.* • Regulatory processes: There is a lack of empirical evaluations of the regulatory processes (e.g. number of trial applications submitted for approval per year, the numbers approved and disapproved, and reasons for the same). ***Action:*** *Included as a gap in the review.* • Ethics of academic clinical trials within medical institutions: Many academic clinical trials happen in medical institutions, including those conducted by post-graduate residents, but they are rarely researched and scrutinized. ***Action:*** *Student-led clinical trials included in gaps.* • Vaccine trial acceptability: There is little empirical evidence as to how vaccine trials are perceived by people and the ethical consideration that inform vaccine developers. ***Action:*** *Included within gaps in the review.* • Therapeutic misconception: Most trial participants experience therapeutic misconception at some level. There is a need to better understand this phenomenon. ***Action:*** *Further emphasised in review.* • Validated questionnaires: There is a need for cross-cultural adaptation (as opposed to translation) of validated questionnaires/tools from other countries, which is sometimes not allowed. For instance, in a study to evaluate osteoarthritis with patient-reported outcome measures, a validated questionnaire asked if the patient can put on and take off stockings, which is not relevant in the Indian context; when asked if that can be changed to sitting or getting up from an Indian toilet, the request was refused. It is likely that similar issues exist for questionnaires used in studies in this review. ***Action:*** *Included as a gap in the review.*
4. Explanations for some of the findings	• Reasons for paucity of RCTs (and nested RCTs or other types of nested studies) in the dataset: Systematic empirical research requires financial support for academics, which is not easily available for researchers in India. Most researchers are expected to carry out research alongside their usual clinical or other duties, and under those circumstances, it is difficult to do research that goes beyond explorations of knowledge and perceptions. Funding and resource constraints mean that although a number of researchers, including those working in the rural areas, are interested in conducting empirical work in relation to informed consent and other ethical issues, their interests often stop at ideation. Many research groups, especially in academic medical centres and government medical colleges, have had to avoid clinical trials as they would be liable to pay compensation for serious adverse events, which they do not have allocated funds for. Drawing from personal experiences, ethics committees have been known to ask investigators to redesign their study, such that it is not a clinical trial, as not many institutions have the funds to provide compensation if necessary. ***Action:*** *Need for funding emphasised in the discussion.* • Some ethical issues are simply not 'researchable' – for instance, corruption and exploitation are difficult to research, but are well captured in the bioethics literature. ***Action:*** *Acknowledgement of the same in the discussion/conclusion.*
5. Concerns	• Ethics committees: Key concerns expressed were in relation to ethics committees, in line with the large number of studies on the same. Concerns revolved around the following issues:

	○ Lack of awareness among ethics committee members regarding good clinical practice guidelines and basic principles underpinning clinical research despite training provision for committee members over many years, making it challenging to assess the nuances related to clinical trials regarding risk minimisation or participant protection. With this being the case in trained ethics committees, there was concern about what may transpire in the case of ethics committees in more remote locations functioning without training. ○ Ethics committees sometimes request investigators to opt for non-trial designs, to avoid institutional liability for compensation if necessary (as outlined in section above). ○ Absence of declaration of roles and conflicts of interest by ethics committee members. ○ Increased workload for ethics committee members, which impedes their ability to examine all the relevant aspects in detail.

Supplementary file 6: Research aims, settings and methods of individual studies

Study	Research aims and setting	Research methods
A. Primary research: Knowledge (or awareness/comprehension), attitudes (or perceptions), practice (or behaviour)		
• **Studies on the comprehension of the informed consent form and/or verbal information provision**		
Arora et al, 2011[62]	To assess comprehension of ICF/IC among participants in a first-in-human study of a novel drug in healthy male volunteers; Chandigarh, India	Questionnaire survey; n=50
Bhansali et al, 2009[65]	To assess comprehension of ICF/IC among patients invited to participate in a phase 3 multi-centric trial of a novel lipid lowering agent; Chandigarh, India	Questionnaire survey; n=42
Figer et al, 2017[78]	To assess comprehension of ICF/IC among participants in a Phase 2/3 rabies monoclonal antibody trial, before and after introduction of mandatory audio-visual recording of IC process in 2013; Mumbai, Maharashtra, India	Questionnaire survey; n=38
George et al, 2018[80]	To assess comprehension of ICF/IC in hypothetical RCTs among adult in-patients with non-organic psychiatric disorders and among their key relatives; Vellore, Tamil Nadu, India	Questionnaire survey; n=32 (14 patients; 18 relatives)
Gota et al, 2018[82]	To assess comprehension of ICF/IC among patients enrolled in Phase 1, 2 or 3 interventional studies; Mumbai, Maharashtra, India	Questionnaire survey; n=200
Joglekar et al, 2013[87]	To assess comprehension of ICF/IC among participants in a cohort study aimed at estimating HIV incidence in a high-risk population; Pune, Maharashtra, India	Questionnaire survey; n=1334
Kamath et al, 2014[91]	To assess comprehension of ICF/IC among medical students invited to participate in a hypothetical anti-malarial drug; South India	Questionnaire survey; n=155
Nambiar et al, 2012[104]	To assess comprehension of ICF/IC among nursing trainees participating in a tuberculosis exposure and latency cohort study; Vellore, Tamil Nadu, India	Questionnaire survey; n=138
Sarkar et al, 2009[117]	To assess comprehension and recall of ICF/IC among parents/guardians of a birth cohort of children from urban slums participating in a diarrhoeal surveillance study; Vellore, Tamil Nadu, India	Questionnaire survey; n=368
Sarkar et al, 2010[116]	To assess comprehension of ICF/IC among parents of children from rural pre-schools participating in an RCT of nutritional supplementation, randomised to receive group or individual counselling for IC; Kaniyambadi, Vellore, Tamil Nadu, India	RCT employing questionnaire survey; n=118 (from 16 rural pre-schools)
• **Studies on Knowledge, Attitudes, Practices in relation to clinical trials/research, research ethics, ethics committees**		
Bhowmick et al, 2014[130]	To assess knowledge, attitudes and practice of ethics committee functioning among ethics committee members; Kolkatta, West Bengal, India	Questionnaire survey; n=30 (from 10 ethics committees)
Burt et al, 2013[69]	To study knowledge and perceptions of clinical research among general public; New Delhi, India	Questionnaire survey; n=175 (from eight public locations)
Choudhury et al, 2016[75]	To assess knowledge and perceptions of clinical trials among doctors from government medical colleges; West Bengal, India	Questionnaire survey; n=133 (from three medical colleges)
Deolia et al, 2014[77]	To assess knowledge, attitudes and behaviour pertaining to research ethics among dental professionals in a private dental institute; South India	Questionnaire survey; n=213
Dhodi et al, 2013[131]	To assess knowledge, attitudes and practices towards clinical research among medical students and teachers; Mumbai, Maharashtra, India	Questionnaire survey; n=395
Gopinath et al, 2014[81]	To assess knowledge and attitudes about research ethics and ethics committees among dental faculty; Chennai, Tamil Nadu, India	Questionnaire survey; n=81

Hussain et al, 2019[132]	To assess knowledge, attitudes and practice regarding informed consent process in biomedical research in postgraduate medical students in a private medical college; Karnataka, India	Questionnaire survey, n=114; Group discussions, n=2 (with 10-12 participants each)
Londhey et al, 2015[97]	To assess awareness of ethics committee composition and functioning among medical teachers; Mumbai, Maharashtra, India	Questionnaire survey; n=180
Joshi et al, 2012[88]	To explore awareness, perceptions of and attitudes towards participating in clinical trials among general public; Pune, Maharashtra, India	Focus group discussions and interviews; n=24 (7 trial participants; 17 non-trial participants)
Joshi et al, 2013[134]	To assess awareness, perceptions and attitudes toward clinical trials and their views on methods to create awareness among general public; Pune, Maharashtra, India	Questionnaire survey; n=240 (40 trial participants; 200 non-trial participants)
Krishna et al, 2014[140]	To examine the relationship between contract research organisations (CRO) and healthy volunteers and the recruitment process in relation to bioavailability and bioequivalent studies; Hyderabad, Telangana, India	Case study of one contract research organisation comprising: Interviews (8 CRO staff); group discussions (n=50 healthy volunteers); observations of informed consent discussions (n=40)
Mallela et al, 2015[98]	To assess knowledge and attitudes about research ethics and ethics committees among dental faculty; North India	Questionnaire survey; n=942
Meenakumari et al, 2010[100]	To evaluate awareness of clinical trials among pharmacy undergraduate and postgraduate students; Manipal, Karnataka, India	Questionnaire survey; n=102
Mishra et al, 2018[101]	To examine awareness of ICMR's ethical guidelines, privacy-relation obligations and experiences in implementing ethics guidelines among ethics committee members; New Delhi, India	Interviews; n=19
Mohammad et al, 2011[135]	To assess knowledge, attitudes and practices of healthcare ethics among medical professionals in a government teaching hospital; Aligarh, Uttar Pradesh, India	Questionnaire survey; n=172
Nadig et al, 2011[102]	To assess knowledge, attitudes and practices pertaining to ethics review and ethical guidelines among ethics committee members; South India	Questionnaire survey; n=29 (from 11 ethics committee)
Ramanaik et al, 2015[112]	To explore knowledge and perceptions of clinical trials (with a focus on HIV vaccine trials) among frontline health service providers working with female sex workers and men who have sex with men; Bellary, Belgaum, Bangalore in Karnataka, India	Interviews; n=50
Reddy et al, 2013[137]	To assess knowledge and attitudes about research ethics and ethics committees among dental faculty; Bhimavaram, Andhra Pradesh, India	Questionnaire survey; n=100
Rodrigues et al, 2013[113]	To assess knowledge regarding knowledge regarding research among HIV-infected individuals; Bangalore, Karnataka, India	Questionnaire survey; n=173
Sridharan et al, 2016[122]	To assess knowledge of clinical trials from semi-urban and rural populations in India; India	Questionnaire survey; n=400
Vittalrao et al, 2018[129]	To assess awareness of clinical trials among medical undergraduate students; Manipal, Karnataka, India	Questionnaire survey; n=257
Vyas et al, 2019[138]	To assess knowledge, attitudes and practices regarding informed consent for research purposes among postgraduate resident doctors; Mumbai, Maharashtra, India	Questionnaire survey; n=100
Thatte et al, 2009[125]	To assess knowledge of compensation clinical trial related injury and among various stakeholders and to review policies on the same; India	Questionnaire survey, n=80 (30 investigators, 23 ethics committee members, 27 sponsors); Interviews, n=14 (3 investigators, 6 ethics committee members, 5 sponsors); Documents, n=119 (informed consent documents)

A. Primary research: Perceptions, experiences, practices/processes in relation to clinical trials/research, research ethics, ethics committees

Bindra et al, 2010[67]	To explore perceptions on research ethics among investigators; India	Questionnaire survey; n=29
Brahme et al, 2009[68]	To study the profile and role of ethics committee members in health and research organisations; Pune, Maharashtra, India	Questionnaire survey; n=52 ethics committee members from 12 committees
Chatterjee et al, 2015[70]	To assess feasibility of informed consent procedure in an RCT for people with schizophrenia, from the trial, research and participant perspectives; Tamil Nadu, Maharashtra and Goa, India	Focus group discussions, n=6; consent interviews and participant feedback on IC process, n=332
Chauhan et al, 2015[72]	To explore acceptability of audio-visual recording of the IC process in a hypothetical study and reasons for refusal; Keezhputhupattu, Tamil Nadu, India	Structured interviews; n=150
Chenneville et al, 2016[73]	To assess perceived capacity of medical school ethics committees through ethics committee members and delineate areas for improvement; West India	Research Ethics Committee Quality Assurance Self-Assessment Tool filled by member secretaries of two ethics committees, n=2; Interviews with committee members, n=6
Davis et al, 2017[76]	To explore perceptions of the 2013 regulatory changes for clinical research among ethics committee members; South and West India	Questionnaire survey; n=25 members from 25 ethics committees
Ganguly et al, 2016[79]	To describe the newly introduced audio-visual recording of the IC process for clinical trials and the perceptions of investigators and trial participants of the same; Gujarat, India	Observations of audio-visual recordings of IC process, n=5; Interviews, n=8 (3 investigators and 5 trial participants)
Gupta et al, 2018[83]	To examine the audio-visual consent process during a Phase 3 rotavirus vaccine trial in healthy infants and parent/guardian participation in the consent process; Chandigarh, India	Audio-visual recordings of consent process; n=100
Hate et al, 2015[84]	To examine key stakeholders' perspectives on data sharing in the context of research involving women and children; Mumbai, Maharashtra, India	Interviews, n=22; Focus groups, n=44 in four focus groups (researchers, managers, research participants, ethics committee members)
Jadhav et al, 2013[133]	To understand perceptions regarding the ethics of clinical research among clinical research professionals; India	Questionnaire survey; n=34 (27 sponsor/contract research organisation staff; 6 ethics committee members; 1 investigator)
Kadam et al, 2016[89]	To assess perceptions of the 2013 regulatory changes for clinical research among clinical trial investigators; India	Questionnaire survey; n=73
Kamat, 2014[90]	To elicit perspectives of stakeholders regarding media representation of their work and ethical issues arising from their engagement in clinical trials; Bangalore, Karnataka and Hyderabad, Telangana in India	Interviews; n=42 (3 sponsors, 7 contract research organisation executives, 19 investigators, 13 ethics committee members)
Kandhari et al, 2013[92]	To provide insights into the structure and functioning of ethics committees from the perspective of ethics committee members; New Delhi, India	Interviews; n=17
Nadimpally et al, 2017[103]	To explore perceptions of clinical trials among trial participants and key informants; Gujarat, Maharashtra, New Delhi, Andhra Pradesh in India	Interviews; n=36
Newman et al, 2015[105]	To elicit perspectives and experiences of key informants involved in community stakeholder engagement activities, in the context of previous HIV vaccine trials in four countries, including India; Chennai, Tamil Nadu, India	Interviews, n=93 interviews; Focus groups, n=140 in 21 focus groups
Parikh et al, 2011[136]	To assess the perceptions regarding the clinical drug trial industry among various stakeholders; India	Questionnaire survey; n=181 (clinical research coordinators/assistants, investigators, managers, directors)

Patel et al, 2016[108]	To explore perceptions regarding the ethical review process and performance of ethics committees among clinical research professionals; India	Questionnaire survey; n=385
Patel et al, 2016[109]	To understand perceptions regarding ethical standards and issues in clinical trials in Indian among clinical research professionals; India	Questionnaire survey; n=385
Rajaraman et al, 2011[111]	To assess extent of participation during informed consent process among parents providing consent for children's participation in an observational tuberculosis study; Palamaner, Chittoor, Andhra Pradesh, India	Observation notes on questions asked by parents during informed consent process; n=4382
Sariola et al, 2015[115]	To explore perceptions of contract research organisations' staff regarding changes in the clinical trial industry since 1995 and 2005, outsourcing of clinical trials to India and models of collaborations; Bangalore, Karnataka; Mumbai, Maharashtra; New Delhi, India	Interviews; n=25 (clinical research assistants, managers, protocol writers, quality assurers, statisticians, CEOs)
Sariola et al, 2019[114]	To explore the role of civil society organisations, academic and public health researchers and health activists in changing the regulations for clinical trials in India; India	Interviews; n=25 (academic public health and medical researchers, health activists)
Simpson et al, 2015[121]	To identify the tensions that emerge for ethics committee members as the capacity to conduct credible ethical review of clinical trials is developed across three countries including India	Interviews; n=14 ethics committee members from India
Vaz et al, 2015[127]	To explore the perceptions, motivations and concerns of the public with respect to participation in clinical trials and biobanking-related research; Bangalore, Karnataka, India	Interviews; n=14
Vaz et al, 2018[128]	To understand views on the ethics of biobanking research among ethics committee members and medical researchers; Bangalore, Karnataka, India	Interviews; n=43 (21 ethics committee members and 22 researchers)
Vaidya et al, 2016[126]	To investigate if coercion is involved in decision-making of medical undergraduate and postgraduate students participating in research; Mumbai, Maharashtra, India	Questionnaire survey; n=300
B. Secondary Research: Reviews of documents		
Bavdekar, 2009[64]	To determine the extent to which issues related to the provision of free treatment and compensation for research-related injury are addressed in the informed consent documents from protocols submitted to ethics committees; Mumbai, Maharashtra, India	Documentary analysis; n=138
Bhide et al, 2016[66]	To evaluate the impact of the 2013 regulatory changes on ethics committee structure, review process, outcomes and administration; Mumbai, Maharashtra, India	Documentary analysis
Chaturvedi et al, 2017[139]	To assess if clinical trials were in line with the health care needs of the country by auditing the clinical trials registry of India	Database analysis (Clinical Trials Registry of India)
Jadhav et al, 2015[85]	To evaluate completeness of ethics application forms submitted for review to ethics committees; Maharashtra, India	Documentary analysis; n=100
Jhanwar et al, 2010[86]	To assess the ease of readability of translated informed consent forms used in psychiatric clinical trials; Varanasi, Uttar Pradesh, India	Documentary analysis; n=30
Kundapura et al, 2013[95]	To assess compliance of informed consent documents with regulations; Pune, Maharashtra, India	Documentary analysis; n=50
Kuyare et al, 2014[96]	To assess queries raised by ethics committees in uninitiated studies and whether these studies obtained ethics approval elsewhere; Mumbai, Maharashtra, India	Documentary and database analysis; n=219 uninitiated studies (minutes of ethics committee meetings) and Clinical Trials Registry-India data
Padhy et al, 2011[107]	To assess compliance of informed consent documents from protocols submitted to ethics committees in relation to the Indian Good Clinical Practice guidelines; New Delhi, India	Documentary analysis; n=300

Patwardhan et al, 2014[110]	To compare the quality and completeness of data and documentation between an investigator-initiated trial and an industry-sponsored study; Mumbai, Maharashtra, India	Documentary analysis and data from 42 patients (28 from investigator-initiated trial; 14 from industry-sponsored study)
Selvarajan et al, 2013[141]	To evaluate the trends in clinical trials in India compared to other countries, and make comparisons to India's disease burden	Database analysis (multiple clinical trial registries)
Shah et al, 2016[118]	To check completeness and find errors in application forms submitted to ethics committees; Bhavnagar, Gujarat, India	Documentary analysis; n=100
Shetty et al, 2012[120]	To review ethics committee application forms for completeness; Mumbai, Maharashtra, India	Documentary analysis; n=445
Shetty et al, 2012[119]	To monitor adherence to protocol and the informed consent process through clinical research site visits by ethics committee members; Mumbai, Maharashtra	Documentary analysis; n=7 site monitoring reports
Marathe et al, 2018[99]	To study the payments for participation allowed by ethics committees and reasons for payments; Mumbai, Maharashtra, India	Documentary analysis; n=227 studies (ethics application forms, protocols, informed consent documents, correspondence of ethics committees with investigators)
Nishandar et al, 2019[106]	To evaluate status of registered, re-registered and accredited ethics committees in India in relation to regulations; India	Database analysis (Central Drugs Standard Control Organization, National Accreditation Board for Hospitals and Healthcare Providers, Clinical Trials Registry of India and Census data); n=1268 ethics committees
Taur et al, 2011[123]	To determine extent to which ethics committees comply with requirements mentioned in guidelines and regulations while issuing letters of approval; Mumbai, Maharashtra, India	Documentary analysis; n=20 (approval letters from 20 ethics committees)
B. Secondary Research: Journal articles		
Bavdekar et al, 2008[63]	To determine proportion of research manuscripts reporting on ethical clearance and obtaining informed consent and/or assent in two paediatric journals published from India	Documentary analysis; n=132 manuscripts
Chaturvedi et al, 2009[71]	To examine whether informed consent and ethical approval were reported in published psychiatric research in one psychiatric journal published from India	Documentary analysis; n=157 manuscripts
Chin et al, 2011[74]	To explore how often journal articles reporting HIV research sponsored by a developed country but conducted in a developing country mention ethics approval from both countries; four countries including India	Documentary analysis; n=50 manuscripts from India
Klitzman et al, 2010[93]	To explore how often human subject research on HIV reported a funding source and conflict of interest in four countries, including India	Documentary analysis; n=79 manuscripts from India
Klitzman et al, 2011[94]	To investigate how often human subject research on HIV reported on ethical approval in four countries, including India	Documentary analysis; n=79 manuscripts from India
Tharyan et al, 2013[124]	To evaluate improvements in Indian journals' editorial policies and reporting quality of RCTs and to compare with reporting quality of protocols in the Clinical Trials Registry-India	Documentary analysis; n=67 Indian medical journals; 145 published trial reports; 768 randomised trials registered on the Clinical Trials Registry-India

Supplementary file 7: Full report of narrative synthesis

A.1. Comprehension of the clinical trial/research informed consent form and verbal information provision in a real or hypothetical research study: Lay (and some professional) participants

Number of studies tagged to topic: 10[62,65,78,80,82,87,91,104,116,117]

Methodological aspects and limitations:

- Comprehension was assessed through questionnaire surveys conducted with sample sizes that were generally small (n ≤ 50)[62,65,78,80] to moderate (n = 100 to ≤ 200),[82,91,104,116] with two larger studies[87,117] (n = 1334 and 368). Most studies, including small-scale, carried out inferential statistics (9/10).
- Most studies were within a single centre. [62,65,78,80,82,91,104] Some did not mention the time period between information provision and comprehension assessment[62,87], with a few conducted more than a year[78,104] to four years[117] after the informed consent interaction.
- Response categories in tools were not clear/not provided in some studies[78,104,116,117], and in others they ranged from multiple-choice questions[62,65] to combinations of categorical and open-ended questions[82,87,91].
- Method of questionnaire administration (6/10), source(s) for questionnaire content (6/10), and whether questionnaire was piloted/validated (5/10) were sometimes not clear or provided.
- Demographic information such as age, gender and education and/or literacy levels were more often provided (although not always) than religion and indicators of socio-economic status such as employment and income.

Synthesised findings:

- Lay group studies (n=8): Participants were reported as comprising a majority of those educated to primary level or more,[65,117] secondary level or higher,[80,82] not completing secondary level[116] or as mostly literate.[78,87] Some studies suggested that lay participants (and/or their relatives) mostly had difficulty understanding or recalling information on the study background,[62] what is a clinical trial,[82] study treatment being unproven yet as the best for their condition,[82] the condition under study,[117] risks[80,87] and benefits[78]. Additionally, in RCTs, randomisation,[65,116] blinding[65] and the need for a placebo[65] appeared difficult to comprehend. A few studies reported that more participants were found to understand that they were taking part in a research study,[87,116] study procedures (e.g. blood samples),[87,116] and confidentiality.[78,87] Study purpose was reported as both well[78] and poorly understood.[116,117] Comprehension on different aspects of autonomy appeared to vary. Some studies indicated that while most participants understood the voluntary nature of participation,[87,116,117] a nuanced understanding of their rights may be lacking as they did not appear to be aware that they were free to withdraw at any point[116,117] or that declining participation would not adversely affect their or their children's regular medical care.[116] In contrast, the rights of participants[62,78,82,87] (such as alternatives to taking part, access to standard care, declining participation or withdrawing)[82,87] were reported to be well understood in some studies.
- Some studies reported that there was no statistically significant variation in comprehension by age,[78,82,87] gender[78,82,87] (except for risk-related information which was better understood by women)[87] socio-economic status,[78,117] income,[65] employment status[87] and time taken for consent.[78] There was variation in comprehension by literacy reported in a large study[87] and no variation in a smaller study.[78] Similarly, there was variation in comprehension by education in a large study (maternal education)[117] and no variation in small to moderate-sized studies.[62,65,82] One study reported no difference in comprehension between patients who were illiterate and those who were educated (non-college or college).[82]
- One RCT that compared group and individual counselling for informed consent did not find a difference in comprehension of key elements between the two groups[116] and an observational study that compared informed consent comprehension scores before and after the introduction of the mandatory AV recording for the consent process found better comprehension after[78] (the duration between consent and questionnaire administration was shorter in the AV group). One study reported that comprehension was significantly higher in pharmaceutical industry-sponsored trials compared to investigator-initiated trials (which the authors have attributed to the elaborate informed consent forms and the lengthier informed consent process in the former).[82] In some studies, the comprehension assessment was used to provide further information to participants on the topics in which they had a lower score,[62,87] with one incorporating a cut-off of comprehension scores ≥ 80% to be eligible for study enrolment (unclear if participants were retested after further information provision). Studies did not explore what may constitute optimal understanding or information provision.
- Professional group studies (n=2): Studies that assessed comprehension in a real cohort study amongst nursing students (undergraduate and postgraduate)[104] and a hypothetical clinical trial amongst medical students (undergraduate),[91] both reported insufficient levels of understanding, although these scores appeared much higher than the scores reported for the lay groups.

A.2. Knowledge of and attitudes/perceptions to clinical trials/research more generally (not in the context of specific studies):

i. Lay participants

Number of studies tagged to topic: 7[69,88,113,122,127,134,140]

Methodological aspects and limitations:

- Amongst the four questionnaire surveys, the larger study (n=400)[122] used descriptive statistics and the more moderate-sized studies (n ~ 175 to 240)[69,113,134] used inferential statistics.
- Two studies administered the same 20-item questionnaire, with Yes/No and True/False/Not Aware response categories to elicit attitudes/beliefs[69,122] that were also reported as knowledge or awareness.
- Aspects such as method of questionnaire administration[122], validation/piloting[134] and source(s) that informed the content of the questionnaire[113] were not mentioned in some studies.
- Demographic information such as age, gender and educational qualifications of participants were generally provided.
- Two were qualitative studies (n=24 and 14)[88,127] that used interviews and/or focus groups, but one study reported the findings descriptively with numerical presentation of results (without an interpretive account).[88] Findings from another qualitative study, where knowledge exploration was not the focus, have also been included here (group discussion with 50 healthy volunteers; other findings from this study have been included in A5 and A6).[140]

Synthesised findings:

- More than half the participants in three of the questionnaire survey studies were educated to graduate level or more[69,122,134] and in the fourth, the majority of participants (72%) had had more than 7 years of education (i.e. at least primary level).[113] Four studies accessed participants primarily from hospital settings[88,113,122,134] and one from public locations.[69] Qualitative studies mostly comprised participants educated to above primary school level[127] and to graduate/post-graduate level.[88]
- Knowledge: Qualitative studies reported that participants (including graduates) who were taking part in clinical research (bioavailability/bioequivalent studies)[140] and those who had not previously taken part in CTs[88] were unaware of what they were or involved (including study name/purpose; only aware that blood would be drawn from them, they may develop rashes or a headache and that they should report other symptoms), that non-English speakers had not heard of the word 'research' and were not familiar with the local translations for the word[127] and that lay participants were generally unaware of the rules and regulations of biomedical research or the role of ethics committees in protecting patient interests.[127] The proportion of participants who said they had heard of clinical trials or clinical research varied considerably across the questionnaire surveys from ~25%[69,134] to 60%.[113] On exploring what participants knew, some studies reported that knowledge was basic[88,113] (i.e. associating clinical trials/research with finding something new) to incorrect among some participants.[134] Those who had heard of 'research' appeared to have positive expectations of it.[127]
- Attitudes: Studies reported that lay participants had overall positive attitudes towards clinical research (i.e. that it benefits community, society, humanity[69,113,122] and is an important step in developing new treatments and advancing medical science[69,122,127,134]), with some noting that participants' main areas of concern were around the protection of participant confidentiality, compensation for participation and adverse outcomes,[69,122] unethical practices in trial conduct[127] (such as fudging data, profiteering, using people as guinea pigs), and lack of trust in pharmaceutical research.[134] Research by academic institutions appeared to be more trusted than those by pharmaceutical companies, with just over half the participants in some studies trusting the government to protect the public against unethical research.[69,122]

ii. Professional participants

Number of studies tagged to topic: 5[75,100,112,129,131]

Methodological aspects and limitations:

- Amongst the four questionnaire surveys, two studies (n=133 and 395) used inferential statistics[75,131] and two (n=102 and 257) used descriptive statistics.[100,129]
- Two studies used the same questionnaire, but the source(s) used to inform questionnaire content was unclear.[100,129] Studies had some explanation of validation/piloting of questionnaires used, but some did not explain questionnaire administration clearly.[75,100,129]
- Demographic information such as education were usually provided but not gender and age of participants in some instances.[100,129]
- Other key information of relevance, i.e., prior clinical trial/research training (curricular or extra-curricular) and experience was usually provided.
- One qualitative study employed in-depth interviews (n=50).[112]

Synthesised findings:

- Studies were conducted with doctors,[75] healthcare students (pharmacology[100] and medicine[129]), a combination of medical students and teachers[131] and Frontline Health Service Providers[112] (FHSPs providing services to female sex workers and men who have sex with men; includes doctors, nurses, counsellors, outreach workers, peer educators, programme managers).
- Knowledge: Studies reported basic level of knowledge of clinical trials/research amongst doctors [75] and medical students and teachers,[131] but lack of familiarity with methodological aspects and regulatory requirements of clinical trials.[131] Knowledge on aspects such as patient confidentiality and rights (e.g. to withdraw after study enrolment and for compensation due to study related injury) appeared adequate[75], while knowledge on aspects such as guidelines, regulations and regulatory authorities appeared inadequate.[75,100,129] The qualitative study with FHSPs found that more than half the participants across different educational backgrounds had little or no awareness of what a clinical trial entailed.[112] Participants were unfamiliar with the English term 'clinical trial' as well as the local translation of the term (similar to lay participants above). Those who had some knowledge of the existence of clinical trials (usually participants with degree level education), admitted to having limited knowledge and some confused clinical trials with routine medical tests and procedures.[112]
- Attitudes: Some studies reported overall positive attitudes to clinical trials/research amongst doctors and medical students/teachers[75,131] (such as 'clinical research is important for the progression of medical science'). Negative attitudes towards pharma or industry-sponsored studies were reported[75] (e.g. majority believed that clinical trials carried out for academic purposes were more ethical/scientific than industry-sponsored trials, patients were exploited and legislations were inadequate in industry-sponsored trials). Clinical trials conducted in India were not considered of good quality by many[131] and there was support for including clinical trials in detail in the undergraduate/postgraduate medical curriculum.[75,131]

A.3. Knowledge, attitudes/perceptions and practices in relation to research ethics (including informed consent): Professional (and some lay) participants

Number of studies tagged to topic: 16[67,77,81,98,101,103,109,126,127,132,133,135-138]

Methodological aspects and limitations:

- Of the 12 questionnaire surveys, seven (n=81, 100, 114, 172, 213, 300, 385) stated they used inferential statistics[77,81,109,126,132,135,137] (but one was reported entirely descriptively;[109] the same dataset was used in another article to report on ethics committees and has been included in section E). Five surveys, including a large one (n=29, 942, 34, 181, 100) used descriptive statistics[67,98,133,136,138] (the findings from the large survey have been minimally used in the synthesis due to discrepancies across numbers/proportions mentioned in tables, results and discussion).[98]
- Details that were unclear/not provided included questionnaire administration,[67,126,132,138] source(s) used to inform questionnaire development[67,98,109,132,133,135-137] and validation/piloting.[109,132,133,136,137] Three studies used similar questionnaires.[81,98,137] It was not always clear if knowledge on the topic was self-reported or objectively assessed.[98,135] Generally, attitudes were better explored and reported on than knowledge.
- Demographic information such as education, age and gender were usually provided (all[133] or some aspects, i.e. age and/or gender, were sometimes not provided[67,109,135,136]).
- In some instances, information was unclear/not provided on whether participants had had prior clinical trial/research training[67,77,98,126,133,135-138] and experience[77,98,133,136].
- One study was reported as a mixed methods study; the reporting of methods and results were however not clear, including the qualitative aspects, so findings have been used minimally in the synthesis.[132] In another study, some questions were not framed clearly and some knowledge questions appeared to assess attitudes[138]. One study was authored by employees of a pharmaceutical company[67] and two studies by employees of clinical research organisations (CROs).[133,136]
- Two qualitative studies employed interviews, one with professional group participants (n=19)[101] and another[103] with both lay (n=32) and professional participants (numbers not available). Lay participant views from this study[103] as well as from another qualitative study[127] (methods included in section A2.i.) have also been included in this section on professional participants as it covers similar themes.

Synthesised findings:

- Four studies were conducted with dental professionals (dental faculty only[81,98] or with dental students and faculty[77,137]); one was with medical professionals (medical students and faculty);[135] and three were with professionals primarily from clinical research organisations/sponsors, but also comprising other stakeholders such as investigators and ethics committee members (henceforth referred to as clinical research professionals for simplicity).[67,133,136] Of the four studies that focused on informed consent, one was with clinical research

professionals[109] and three were conducted with medical students.[126,132,138] One qualitative study explored ethics committee members' views on issues such as ethical guidelines.[101] A further two qualitative studies were primarily with lay participants - focused on clinical trial participants' experiences of participation[103] and on biobanking and biomedical research in general[127] (the only two lay participant views included in this section).

- Knowledge:
  - *Research ethics:* Studies reported that there appeared to be gaps in self-reported knowledge (i.e. where participants where asked if they were familiar/aware of a particular topic or not) of research ethics[81,137] or poor actual knowledge[77] (i.e. when reported as tested/assessed, although unclear what questions were asked) amongst dental professionals.
  - *Ethical guidelines:* Self-reported knowledge on national/international guidelines for research ethics was noted to be poor among dental[98] and medical professionals.[135] Ethics committee members (from 11 committees) in a qualitative study were generally found to be aware of national ethical guidelines (but not international).[101]
  - *Informed consent:* One study reported that knowledge of informed consent was good as all participants (medical students) knew that informed consent: was not only verbal consent, should include information that it is a research study, includes patient autonomy to withdraw at any time, is mandatory in prospective studies and should not be obtained with undue inducement. Most medical students were also noted as being aware that informed consent includes aspects such as study duration, information on risks/benefits of participation, statements on confidentiality/privacy and is mandatory in observational surveys.[138] In general, studies reported that medical students had good knowledge of informed consent but poor attitudes and practices in relation to the same.[132,138] In a qualitative study with clinical trial participants (lay group), some appeared confused between the signing of the informed consent form and filling of the questionnaire for the trial.[103] In another qualitative study with lay participants, to most respondents, 'to consent' meant 'to agree' and that this was done by signing (however, this was in general seen as providing protection to the doctor/researcher/hospital than the patients).[127]
- Attitudes:
  - *Research conduct:* There appeared to be some support, amongst dental professionals, for fabricating data to improve research outcomes if it did not harm patients (ranging from 12% to 44%).[81,98,137] A fifth of resident doctors appeared willing to undertake research that was rejected by ethics committee.[135] There was all round support for the need to protect confidentiality of participant data and to take measures to prevent accidental exposure of patient data.[81,98,137]
  - *Informed consent:* Some ethics committee members felt that the informed consent form was merely a tool to obtain signatures, it was often not read to patients and not in local languages.[101] Similarly, more than half the clinical research professionals felt that the informed consent process does not truly inform patients and is focused on legal compliance.[67] More than 90% of dental professionals were in favour of informing patients of the risks and benefits of research,[81,98,137] always including the patient's signature as part of informed written consent, seeking informed consent when involving patients with invasive procedures and for the use of biological samples (but lesser support in relation to blood samples, 78% and 44%).[98,137] Most post-graduate medical students ($\geq$ 80%) believed that informed consent should be explained in the local language, be obtained before the start of research work and patients should be allowed to withdraw after signing informed consent; fewer (66%) believed that a witness was absolutely necessary during informed consent.[138] Majority (> 80%) of clinical research professionals believed that participants were offered the opportunity to ask questions, were able to refuse participation[133] and had full understanding that there was no compulsion to participate,[67] although very few from the same group believed that patients were truly autonomous.[67] Most clinical research professionals in another study believed participants did not have full understanding that there was no compulsion to participate[109]. More than half of clinical research professionals believed participant rights and alternative treatment options were explained during the informed consent process and about half felt patients were adequately informed about trial participation and informed of risks,[133] but most clinical research professionals in another study believed participants were not properly informed of risks.[109] Many clinical research professionals believed that the informed consent process should be monitored by ethics committees or patient research advocates.[109]
  - *Informed consent forms:* Most clinical research professionals had concerns about information on funding on informed consent forms, along with information provided on study purpose, possible risks/benefits and right to withdraw; they believed forms should be simplified and include pictorial images.[109]
  - *Research ethics education:* Most dental professionals were in support of research ethics education for postgraduate students, investigators and ethics committee members.[81,98,137]
  - *Clinical trial drug industry:* Most clinical research professionals believed that the industry in India is growing, but that India is not utilising its full potential and delays in regulatory approvals were a key hurdle to the growth of the clinical trial industry in India (lack of trained investigators/site staff, unethical practices and public awareness also selected as hurdles by many, but lack of patient population and increasing costs of clinical research in India were not).[136]

- Practices: One study reported 'unsatisfactory' behaviour in relation to how frequently dental professionals used scientific journals/internet regarding research ethics, whether they maintained accurate patient records for research and whether they attended training programmes in research ethics.[77]
  - *Informed consent:* Majority of medical professionals had obtained written informed consent during research.[135,138] Proportion who did this in the local language varied (≤ 50%[135] to > 80%[138]). The majority (> 80%) of medical professionals in one study stated that they obtained the signature of an impartial witness alongside that of participants' on the consent form, handed over the participant sheet while obtaining informed consent and explained to participants that they were in a research study[138]. In another, only a third of medical professionals reported taking consent in the format advocated in national guidelines[135] and far fewer (~ 12%) provided a written copy of the written consent to patients.[135] There was no research on what information recruiters usually discuss in an informed consent interaction or what patients expect to be informed about.
  - *Coercion:* In one study that explored if medical students felt coerced into research participation, a quarter of participants stated they had participated in research study/studies due to faculty requests, a few did not know they could refuse participation, a third disagreed that participation was entirely their own choice and two-thirds said they had participated despite not wanting to. Majority also felt that faculty would like it if they participated and that it will help their academic grades. Overall, authors concluded that medical students felt under pressure to participate in research studies and were concerned about the repercussions of refusal.[126]
  - *Experiences of informed consent process (lay participants):* Some clinical trial participants in a qualitative study stated that they were not given detailed (or sometimes any) information about the trial before enrolment and that the benefits of the drug being tested were sometimes emphasised and presented as the best option available. Many said they had signed the consent form without understanding the contents as they trusted their doctor. All participants appeared to be aware of their right to withdraw, but their accounts indicated that their decision making for participation may not have been truly autonomous and voluntary (mediated by factors such as gender norms).[103]

A.4. Knowledge, attitudes/perceptions and practices in relation to Ethics Committees (including composition, functioning, performance, capacity, review process): Professional (and some lay) participants

Number of studies tagged to topic: 18[67,68,73,76,81,89,92,97,98,101,102,108,121,127,130,133,135,137]

Methodological aspects and limitations:

- Of the seven questionnaire surveys, three used descriptive statistics (n=25, 73, 29)[76,89,102] and four used inferential (n= 52, 180,385, 30),[68,97,108,130] of which one was reported entirely descriptively.[108]
- Some information was usually provided on questionnaire administration, with information being limited[97,102,130] or unclear/not provided[68,76,108] on validation/piloting; and unclear/not provided on source(s) used to inform questionnaire development.[76,97,108,130]
- Demographic information was not always provided on education[76,130], gender[76,89,97,108,130] and age[76,97,102,130] of participants.
- Information was sometimes not provided on clinical trial/research training[76,89] and clinical trial/research experience.[76,97,102,130]
- Three qualitative research studies employed interviews (n=6, 17, 14).[73,92,121]
- (Note: Methodological aspects of seven studies included in the synthesis here are within the previous section, A3[67,81,98,101,133,135,137] Also, findings from one study with lay participants that briefly explored views on ethics committees is included here[127]).

Synthesised findings:

- Questionnaire surveys were conducted with dental professionals (dental faculty only[81,98] or with dental students and faculty[137]); medical professionals (medical students and faculty[135] or medical faculty only[97]); ethics committee members,[68,76,102,130] and clinical research professionals (comprising investigators from contract research organisations/public hospitals with/without ethics committee members and sponsors).[67,89,108,133] Four qualitative studies were with ethics committee members[73,92,101,121] and one was with the general public.[127]
- Knowledge: *Ethics committee composition and functioning:* Self-reported awareness (i.e. where participants where asked if they were familiar/aware of a particular topic or not) of the functions of ethics committees amongst dental professionals[81,137] and self-reported awareness of the composition of ethics committees amongst medical professionals[135] were both reported to be limited. Majority (56%) of medical faculty in one study were reported to have below-average to average actual knowledge (i.e. when reported as tested/assessed) on ethics committee composition and functioning (explored quorum requirements, member composition, lay representation, frequency of meetings, submission deadlines).[97] In another study, ethics committee members were reported to be aware of the requirement of a quorum to conduct a meeting, but not how many members constituted a quorum.[102] Some

studies asked whether participants knew of the presence of any ethics committees and reported that the majority did.[81,135] Lay participants in a qualitative study were reported as unaware of the role of ethics committees in protecting the interests of research participants or in addressing the violations of their rights.[127]

- Attitudes:
  - *Ethics committee functioning:* There was widespread support for the existence and need for ethics committees among dental professionals,[81,98,137] but limited satisfaction amongst medical professionals and clinical research professionals regarding ethics committee functioning in some studies[108,135] and high levels of satisfaction in others (with clinical research professionals).[67] About half the clinical research professionals scored ethics committees 5 or over (on a scale of 1 to 10) in relation to their independence[133]. Conflict of interest was considered a key reason for committees' lack of independence[133] and as a barrier to committees' functioning by investigators.[108] Pressures from senior management was also considered a reason for committees' lack of independence by clinical research professionals in one study,[133] but only few felt that pressure from sponsors was a barrier faced by ethics committees in another study[108]. Majority of ethics committee members felt that the committees' functions should include mediating between the media and researchers, monitoring serious adverse events, ensuring the community benefits from the research,[68] protecting patient confidentiality and imparting research ethics education to investigators.[101] Most clinical research professionals believed that auditing ethics committee performance by third parties and the registration of ethics committees will improve the functioning of ethics committees and ethical standards.[108]
  - *Regulatory changes:* Ethics committee members discussed the evolution of stricter guidelines for how ethics committees function and felt that the 'bar has risen' over time.[121] In another study with ethics committee members from 25 committees, members were in support of regulatory changes (of August 2016, where ethics committees have to take responsibility for decisions such as the number of trials per investigator), but felt that the changes were too many, too often and a burden to committees.[76] While most ethics committee members stated feeling empowered to take a decision on approving the number of studies per investigator,[76] fewer investigators were in favour of restrictions on trial numbers allowed per investigator.[89] Ethics committee members felt that there was lack of clarity on the role of independent ethics committees.[76] *Accreditation/registration:* Most ethics committee members were in favour of accreditation for all committees, but identified challenges they encountered with the process for renewal of registration of ethics committees (such as lack of clarity with requirements and cumbersome documentation, lack of institutional support and resource constraints and lack of acknowledgement after submission of documents). [76]
  - *Ethics committee composition:* Most ethics committee members felt that the committees should be reconstituted every two years and that those invited as members should be experts in their field and trained in ethics.[68]
  - *Ethics review:* In general, majority of dental professionals supported the need for ethical review for all human research,[81,98,137] except surveys and retrospective studies (this was amongst dental and medical professionals).[98,135] In the same vein of support for ethical reviews, majority of dental professionals disagreed that ethics approval was not necessary due to the presence of scientific committees[81,98], ethics approval delays research and makes it harder for researchers[81,98,137] and ethics review should be restricted to international collaborative research.[81,98,137] Two-thirds of ethics committee members (of 25 committees) believed that the scientific review committees and the ethics committees should be kept separate.[76] Most, but not all, ethics committee members disagreed with trials starting before ethical approval to save time.[102] More than half the clinical research professionals did not feel that the safety review by ethics committees was adequate.[133] Most clinical research professionals felt the ethics review process benefits research, but also that ethics committees failed to understand research protocols/methodology and sometimes over or under estimated risks of clinical trials.[108] The notion of 'ethics committee shopping' was discussed by committee members, where investigators/sponsors went elsewhere if refused approval at the first.[121] There was overwhelming support for a single national research ethics committee to consider multicentric trials amongst clinical research professionals,[89,108] which is likely to help prevent 'ethics committee shopping', but there was less support for this amongst ethics committee members.[76]
  - *Research ethics/GCP training:* Majority of ethics committee members[68,92] and clinical research professionals[133] were in support of research ethics/GCP training for ethics committee members (although fewer, i.e. ~ 40%, ethics committee members were in support of this in another study[102]). Clinical research professionals also supported wider training for ethics committee members, for example, in regulations and roles/responsibilities of each member.[108] Some ethics committee members stated that training was challenging to organise for doctors who were busy and that doctors may not require intensive ethics training as they were already sensitised to patient issues and aware of the role of ethics in clinical research.[92]

- *Ongoing monitoring and on-site visits:* Ethics committee members from 11 committees in one study were in support of ongoing monitoring of trials by ethics committees,[102] while in another study members from five committees were not in support of this and believed monitoring should be the responsibility of third parties or sponsors/investigators.[92] Most clinical research professionals believed that improving the review process through on-site visits will contribute towards improving the functioning of ethics committees.[108]
- *Guidelines/regulations:* One qualitative research study suggested that ethics committee members intense focus on informed consent, guidelines, legality and regulations in their accounts may be because this was a way for committees to gain credibility amongst researchers; strict proceduralism was felt to overtake protection of participants' interests and being humanistic.[121] Another qualitative study provided an example where institutional bias was observed (the use of a placebo in a trial was discussed in relation to protecting the institute's interests rather than as a moral dilemma) and that participant protection was often the by-product of the need to safeguard an institution's legal accountability.[92]

- Practice:
  - *Ethics committee functioning and composition:* Members from eleven ethics committees reported that they function independently and with appropriate representation of people with different qualifications as stipulated by national guidelines.[102] Most ethics committee members scored themselves above 5 (one a scale of 1 to 10) in relation to their involvement in meetings and those from non-medical backgrounds mostly stated that they did not feel restricted by their background while participating in meetings.[130] Most ethics committee members (from five committees) noted that there was an arbitrariness in member selection, with no policies on selection and reliance on informal networks, especially for members not affiliated to the institutions in which the committee is based. Members affiliated to the institutions, on the other hand, appeared to have limited choice in refusing membership in a committee[92]. Two ethics committees scored 62% and 67% on a quality assurance self-assessment tool for ethics committees.[73]
  - *Ongoing monitoring and on-site visits:* Nearly all ethics committee members from 11 committees said they undertook periodic ethics reviews of ongoing trials, but far fewer said on-site monitoring was conducted.[102] In another study members from five ethics committees said they did not undertake monitoring of ongoing trials.[92] Nearly two-thirds of committee members (of 25 committees) said they did not have a well-devised plan to visit sites for monitoring during study conduct and just over a third stated that their committees had visited sites for monitoring ongoing studies.[76] Ethics committee members from two committees in another study said they required annual and end of study reports from investigators.[73] Members from 11 committees in a qualitative study highlighted variations in practice.[101] Some (contrary to national guidelines) did not see committees having a role in ongoing monitoring of research conduct and management of information and explained that their role was over once approval was granted. Others stated they intermittently investigated whether studies were carried out appropriately.[101]
  - *Workload and working patterns:* The increasing workload of ethics committees was frequently discussed across studies, including that limiting the total number of trials handled by committees will improve its functioning.[108] Some reported the frequency of meetings across ethics committees (once/week to once/two months[102] or 25-70 per year[73]), the number of protocols reviewed per meeting (1 to 20 per meeting;[102] 50 protocols once/month in ethics committees of public hospitals versus 2-6 protocols once/month in those of private hospitals)[92] or the number of meetings attended per year by members (1 to 10 per year).[130] Some public hospital committees appeared to combine the scientific and ethical review at their meetings and were reported as having lesser administrative support than those in private hospitals.[92] Most members from 11 committees stated that they received proposals two weeks in advance of the review meeting, results were communicated to investigators within a week and that all documents were archived for five years.[102]
  - *Ethical review:* One study raised in detail the dilemmas faced by ethics committees in India (as well as Sri Lanka and Nepal) in relation to the growth of pharma industry (pharmaceuticalisation) and the ethical review process. Committees face increasing the pressure to assimilate within the international standards of ethical review, while also being cognisant of their larger responsibilities towards protecting not just research participants but also national interests[121] (for instance, in ensuring research does not reinforce existing health and social inequities).
  - *Honorarium:* Most ethics committee members (from 11 committees) said they received an honorarium for their time.[102]
  - *Documents reviewed:* Amongst two ethics committees studied, both were reported as having a policy for how protocols were reviewed, when members received the protocol and supporting materials for review, but only one had a checklist for documenting their ethical assessment.[73]
  - *Aspects reviewed:* Some committee members outlined the privacy/confidentiality[73,101] and informed consent[73] aspects that were considered by investigators and reviewed by ethics committees (i.e. how data collected was protected, whether lock and key or electronic; process/setting of obtaining informed consent; reading level of informed consent forms; and whether they covered the basic elements of informed consent).[73,101]

- *Guidelines followed:* There appeared to be variations in how and which ethical guidelines were followed by ethics committees.[101] All ethics committee members (from 11 committees) stated they followed national guidelines (ICMR), but fewer mentioned international guidelines (e.g. ICH-GCP, WHO GCP).[102]
- *Training:* Ethics committee members recognised that they had high training needs and majority of members (from 25 committees) said that their committee has a training plan and members are trained when there are new regulations.[76]

A. Primary research: Perceptions, experiences, practices/processes

A.5. Informed consent processes: Lay (and some professional) participants

Number of studies tagged to topic: 13[70,72,79,83,111,140] including findings from seven studies[76,78,89,103,109,127,133] where the focus was not on informed consent

Methodological aspects and limitations:

- One large (n=4382)[111] quantitative study was based on observations of informed consent discussions and the other was a questionnaire survey (n=150)[72], with both employing inferential statistics.
- Of the three qualitative studies, one employed interviews (n=8) and observations of consent interactions (n=5)[79], another involved audio-recordings of consultation recordings (n=100)[83] and the third was a case study of a contract research organisation (CRO) conducting bioavailability/bioequivalent (BA/BE) studies, comprising interviews with CRO staff (n=8), group discussion with healthy volunteers (n=50) and observations of informed consent discussions (n=40).[140]
- A mixed methods study involved a questionnaire survey (n=332; descriptive) and one focus group discussion.[70]
- Methodological aspects of the additional seven studies[76,78,89,103,109,127,133] are in other sections.

Synthesised findings:

- Studies were mainly conducted with lay participants (general public,[72] healthy volunteers in BA/BE studies,[140] potential clinical trial participants,[70,79] including parents of children[83,111]). Three studies also included views of researchers[70,79] and CRO staff.[140]
- Only one study described the process of customising the informed consent process to the trial population. The informed consent procedure for an RCT with people with schizophrenia was developed with prior feedback from participants/caregivers, incorporated the feedback received (such as simplifying the information sheets, developing a flip chart with diagrams to explain key study elements, making the consent procedure more interactive) and then evaluated the feasibility of this informed consent process from multiple perspectives. The informed consent process and the use of the flip chart were found to be useful by participants and study personnel. Study personnel found the manual-based training and ongoing support to be helpful and noted that concepts such as trial, research and randomisation were difficult to convey and required considerable time to explain.[70]
- <u>Patient participation in informed consent discussions:</u> The questions asked by parents/guardians of potential child (infant) participants during discussions varied from 13% in a study where the discussions where preceded by a community information session (study physicians/research nurses were not involved in consent process; study personnel trained on ICH-GCP guidelines were instructed to encourage questions from participants and note down questions/comments at the back of the consent form when questions went beyond simple clarifications of informed consent form; study was conducted by an organisation that has provided charitable health services in the community for more than 30 years)[111] to 55% in audio-recordings of consultations.[83] Most frequent questions asked include who to contact in an emergency, risks to child, questions specific to the condition being studied (such as tuberculosis) and benefits to child/family of participants.[83,111] Education,[83,111] higher socio-economic status, and the presence of both parents were associated with asking questions.[111] Some participants in a qualitative study (interviews exploring hypothetical trial participation), especially those who were less educated and did not know the meaning of research, stated that they would not ask the doctor any questions about the trial, despite lacking sufficient information.[127] In a qualitative study of healthy volunteers for BA/BE studies, observations of informed consent discussions revealed that the volunteers' concerns revolved mainly around the payment they would receive for participation than about their own health.[140]
- <u>Recruitment process/experience and informed consent process:</u> A qualitative study that examined a CRO as a case study found that healthy volunteers were recruited for bioavailability/bioequivalent studies through lists created through networks and middlemen who are paid a commission for recruitment. These volunteers constituted a pool of readily-

available participants regularly approached for participation, with many volunteers exceeding the maximum number of studies they are allowed to participate in per year. CRO staff stated that some CROs have systems in place to thwart such irregularities, but others did not, facilitating serial participation. CRO staff also noted that most volunteers had decided to participate much before they attended the informed consent discussion or saw the consent documents, with the subsequent informed consent process being a mere formality. Contrary to accounts of family-based models of informed consent being the norm, volunteers were unaccompanied during discussions and nearly all (48/50) said they decided to participate in the bioavailability/bioequivalent studies without informing their families as they would not allow the volunteers to participate and would see the volunteers as selling their bodies for money.[140]

- Audio-visual (AV) recording of informed consent discussions:
  - *Acceptance:* In a study that used a hypothetical scenario to assess acceptability, a third of the (lay) participants refused consent for AV recording of consent,[72] whereas nearly all (lay) participants who expressed an initial willingness to participate in a real vaccine trial agreed to undergo AV consenting process.[83] In a study where AV recording process was observed, it was noted that patients and investigators were uncomfortable (self-conscious) due to the process,[79] whereas authors in another study noted that while patients seemed intimidated by the AV consent process at the beginning, they became more relaxed and comfortable after it was explained and they started to participate in it.[83]
  - *AV process:* Consent discussions that were audio-recorded were described as being undertaken in private spaces[79,83], without any other individuals present[79] or with an impartial witness if the patient was illiterate,[83] after separate consent for AV recording,[79,83] with recordings stored with password protection.[79] Time taken for the AV process varied from 30-45 minutes[83] to an hour-and-a-half to two hours.[79]
  - *Perceptions of AV recording:* Support for the AV recording process among professionals varied (nearly two-thirds of clinical research professionals,[133] just over a third of investigators[89] and investigators in general in a qualitative study[79] were reported to be in favour of the AV recording of informed consent). Investigators expressed concerns about the lack of guidance and training to support them[79] and investigators and patients were concerned about the extra time that was required to undertake the AV consent process.[79,89] Key informants (investigators, from sponsor/contract research organisations, ethics committee members) and patients had privacy and confidentiality concerns with the process.[79,89,103] Other concerns included that it may cause anxiety and discomfort amongst participants and that it would affect large-scale community studies.[89] Some authors reported that they did not have the commonly reported problems of lack of infrastructure or any issues around sound quality, training of personnel and storage/retrieval of recordings.[83] More than three-quarters of ethics committee members from 25 ethics committees felt that the informed consent process was adequate in their institutions, but less than half stated that their ethics committees review AV recordings if there were reports of noncompliance/protocol deviations in the informed consent process.[76]
  - *Role in improving informed consent:* Only few investigators believed that the AV recording of consent process would improve informed consent in one study.[109] However, there was a notion amongst some investigators (and study authors) that the AV recording of informed consent process increases investigator responsibility, accountability and transparency of the process, and that it provides legal protection to participants.[83,89] An observational study that compared informed consent comprehension scores amongst participants before and after the introduction of the mandatory AV recording for the consent process found better comprehension after[78] (the duration between consent and questionnaire administration was shorter in the AV group).

A.6. Bigger picture: Professional (and some lay) participants

Number of studies tagged to topic: 20 (studies and themes that covered cross-cutting ethical issues are included here)

- Seven studies (not included in above sections) that explored larger issues were mostly qualitative studies employing interviews or interviews with focus groups (n=66, 42, 83, 25, 25, 43 participants)[84,90,105,114,115,128] and one mixed methods study (n=80 questionnaires, 14 interviews, 119 informed consent documents).[125]
- Findings from a further 13 studies[67,75,76,90,92,103,108,109,112,127,130,133,140] (methodological aspects included in sections above) that touched upon these larger themes have also been included in this section.

Synthesised findings:

- The seven key studies included here were primarily conducted with professional groups, such as staff from contract research organisations (CROs),[90,115] EC members,[84,125,128] (including judges, social workers, bureaucrats, medico-legal experts),[90] trial sponsors,[90,125] investigators/researchers,[90,125,128] (including academic public health/medical researchers and health

activists from non-governmental/civil society organisations)[114] and employees or participants in research conducted by non-governmental/community organisations.[84] One study included participants from both professional (key informants such as representatives from civil society organisations, community leaders, advocates, services providers, trialists) and lay groups (community members, former trial participants and individuals from HIV high-risk groups).[105] Similarly, of the further 13 studies that have been drawn from, all except two[103,127] were with professional groups and one was with professional and lay participants.[140]

- Compensation (n=10):
  - *Free medicines/vaccines/treatment and post-trial drug access:* A qualitative study reported that lay participants who were educated and from high socio-economic groups felt that the product (vaccine) should be free to motivate participation as it is still being researched and not on sale. However, 'free' meant inferior or dangerous, especially to some from lower socio-economic groups, who compared it to government hospitals being free and providing poor services.[127] There was mixed support for post-trial drug access amongst doctors,[75] investigators[67] and clinical research professionals[133] with many but not all supporting it (in two of these studies, majority of respondents were from industry/private sector and the study authors were from a pharmaceutical company[67] and a contract research organisation[133]).
  - *Payment for participation:* Amongst lay participants with a poorer understanding of research and a higher therapeutic misconception, payment for participation was not acceptable. Some were also sceptical that being paid would mean the sponsor would have lesser responsibility towards them, thereby making the participant more vulnerable. Others felt it was their right or their due, a way of showing appreciation for taking part, an important way to compensate for potential risks/inconvenience, an incentive and a way to make the participant accountable.[127] In another study, investigators supported a reasonable daily/travel allowance for the study visits and emphasised the need to reassure patients that they would not have to pay from their own pockets.[67] In a qualitative study, healthy volunteers were observed bargaining for incentives that were much higher than what was in the protocol and approved by ethics committees.[140]
  - *Payment for researchers:* Amongst lay participants whose motivation for research participation was altruism, there was little support for payment for doctors/researchers to conduct research as they felt that doctors/researchers should also have the same attitude, especially if they were already being paid for their jobs and where the patients' participation was voluntary. Payments for doctors/researchers was felt to be particularly unethical if they were paid per patient recruited. Others felt it was fair for doctors/researchers to be paid for their research work but that this should be reasonable, and were in support of transparency and disclosures regarding payments for doctors/researchers.[127]
  - *Compensation for study-related injuries/serious adverse events:* Most clinical research professionals (sponsors, investigators, ethics committee members) were aware of the Indian laws and guidelines regarding compensation for clinical trial related injuries, but far fewer said they were compliant with them or implemented them.[125] On the other hand, a qualitative study with a similar participant profile reported that key informants (sponsors, investigators, ethics committee members, contract research organisation representatives, programme managers) lacked clarity on the provision of insurance and compensation for trial related injuries and trial participants were completely unaware of compensation arrangement or insurance provisions for trial-related injuries[103] (note: both studies were conducted prior to the introduction of new regulations on compensation in 2013). Most (not all) clinical research professionals (investigators, ethics committee members, sponsors) were in favour of compensation for trial-related injuries/serious adverse events, the new regulations on them and felt able to navigate the stipulated processes, calculations and timelines in relation to these.[76,89,103,133] One study reported that while most clinical research professionals supported compensation for travel, fewer were in support of payments for participants' time, study risks, inconvenience caused by participation or as an incentive for participation.[109] Ethics committee members stated that they did not have the time or the expertise to review compensation plans for trials, although they felt it was important. Also, most were reported as not being aware of the details of insurance contracts, although their review and approval was part of committee members' responsibilities.[125] Some ethics committee members felt that compensation determination should be outside the remit of institutional ethics committees, that defining risk in the compensation formula was challenging and were in support of training for members on the topic.[76] Studies conducted before the new regulations reported that the PI, sponsor and EC members were involved in deciding the level of compensation based on various factors (such as number of dependents, age, type/stage of disease, etc)[103] and that compensation appeared to be limited to acute management of adverse events during the trial (which the patient has to pay for and would be compensated later); clinical research professionals did not mention compensation for lost wages during the adverse event/death and permanent disability, even thought it is mentioned in the national guidelines.[125]

- *Adverse event reporting:* A qualitative study reported that key informants lacked clarity on the timelines and process for reporting adverse events. The study reported that in practice it appeared that trial participants were given a list of possible adverse events and numbers to contact if they occurred, but some participants did not report these and sought help from local doctors, which meant they were not reimbursed for their expenses. The authors noted that most adverse events were not recorded as linked to clinical trials and that it appeared that most were recorded primarily for reporting purposes (e.g. to sponsor).[103]

- Sharing of data, blood/tissue samples, results and benefits (n=3): In general, findings acknowledged that there appeared to be limited experience of data sharing and it was perceived as a new territory, amplifying participants' reservations.[84]
  - *Blood/tissue samples sharing:* Lay participants in a qualitative study on clinical trials and biobanking research initially readily agreed to have their blood/tissue samples stored for future research/sharing (as it was 'outside the body' anyway, was a 'waste' for the individual, etc), but were more discerning when probed and given further information.[127] Participants were generally positive about samples being used for future genetic research, but concerns were expressed regarding misuse of samples, ethical issues, commercial exploitations, manipulation of nature and eugenics.[127]
  - *Medical records/clinical data sharing:* This was perceived as non-controversial by lay participants as long as they were used for beneficial purposes and confidentiality was maintained; some however preferred being informed about the reason the records were needed (participants were unaware of legal position on sharing of personal data). While some participants felt that anonymising data would make the sharing of illness/medical history acceptable, others preferred restricted disclosure only to those concerned with research, mainly due to concerns regarding security of electronic information and the stigma around certain health conditions (despite this, participants appeared to prefer being contactable in the case of genetic research, where there was a possibility of individual findings being shared).[127]
  - *What is data?:* The meaning of 'data' was explored in a qualitative study with researchers, managers and research participants (mixed population group comprising professional and lay participants) associated with non-governmental organisations.[84] Data was perceived as including but not limited to demographic/household details, images, videos, medical records and both qualitative and quantitative information. All data was perceived as possibly sensitive as it may have the potential to harm an individual/community/organisation (e.g. HIV status, sexual behaviour), but this mixed population group felt that data could be shared if anonymity could be guaranteed.[84]
  - *Benefits/harms of data sharing:* Benefits of data sharing discussed in the mixed population group included evidence generation, increasing transparency/validity of findings, avoids duplication of efforts and burdening participants with similar research and encouraging learning. Harms of data sharing were mainly the misuse of data, primarily for commercial activities and market research, and the potential for harm to patients/communities, even if data were anonymised, especially when the aims of the data accessor was not clear. It was also felt that participants may refuse to participate in a study or provide incorrect information if they were aware that data may be shared with third parties that they do not know of.[84]
  - *Barriers to data sharing:* Lack of experience, competitive working environments, scepticism of the motives of data accessors and the work required to clean and share data, especially qualitative data were all discussed as barriers to data sharing amongst lay and professional participants.[84] Lay participants indicated that not knowing the individual/institution that would access their data later made it difficult to trust them.[127]
  - *What could help?* Some participants (lay and professional) felt that data sharing would be acceptable when it was with reputed institutions, where it was managed rather than open access to data and with governance/policies in place, including on sharing, authorship, payments, ownership and protection of data from misuse.[84] Lay and professional participants also felt that data sharing was justified if it directly led to interventions or solutions to health issues rather than when it was simply used to write articles (some argued that it would be okay to share data even without direct community benefit if it meant others would learn from it).[84]
  - *Confidentiality:* There was agreement that this was key,[128] with the responsibility for this laying more with the data sharer (i.e. initial researcher) than with the data accessor (i.e. who later requests for access), as the participant trusted the researcher they initially provided consent to.[84] However, this was acknowledged as particularly difficult for qualitative research.
  - *Payment for samples:* Ethics committee members and medical researchers in a qualitative study discussed the ethical dilemmas around paying participants for samples.[128] While making profits out of someone's sample while excluding them from the benefits was not deemed acceptable, being paid was seen as equivalent to tissue trafficking and tissue

being seen as a commercial commodity. Some felt that paying participants could lead to unethical practices, while others felt that it was not acceptable to expect one-sided altruism from participants. They argued that payment for contribution is fair as participants have a right to monetary benefit, especially when the samples led to commercial development and benefit (as opposed to academic research).[128]

- *Benefit sharing:* Lay participants spoke of a community development approach (which involves giving back to the community/medical field, for e.g. through low-cost healthcare) and a participant focussed approach (as the individual agreed to take part when there was uncertainty around the drug) to sharing the commercial profits that were gained by pharma companies after a successful research study.[127] Similar views were expressed by ethics committee members and medical researchers (giving back to the community by supporting further research or healthcare provision in the area, especially when outcomes of studies are commercialised for profits).[128] Giving back to the community as opposed to directly to the individual was also seen as a way of protecting individual confidentiality.[128]
- *Sample ownership:* In the context of biobanking research, sample ownership was seen as a grey area by ethics committee members and medical researchers. It was seen as the patients' (as the needs/interests of the sample contributor were of utmost importance), custodians' (where the storage facility/department/laboratory was the technical owner with responsibility for safe-keeping and prevention of misuse), and the researchers' (as the consent form transfers the ownership from the sample contributor to the researcher). There was also some limited discussion of the difference between ownership of samples/clinical data as opposed to ownership of research data, with former belonging to the patient and latter to the researcher.[128]
- *Disclosing individual findings:* This had not been given much thought of by most ethics committee members and medical researchers, but generally respondents felt that actionable individual results that have clinical significance should be made available to the sample contributor. These views were recognised as being different to countries like the United Kingdom (where individual results were not shared with the contributor), but given the lack of universal health coverage/health insurance and the socio-economic context in India, letting the sample contributor know their results was seen as a way of 'giving back'. It was acknowledged that the mechanisms to carry out this out may be challenging, with suggestions for who could do this ranging from the treating physician, counsellors, social workers or through a special facility that would liaise between the sample contributor and researchers to convey findings and provide counselling (via social workers, not medics).[128] The views of participants regarding disclosing individual findings following biobanking research varied from being unsure (reasons: consent not taken/discussed beforehand, confidentiality violation/sensitive issues, difficulties with insurance), definitely no (reasons: treatment and research are different, findings are irrelevant to patient care, possibility of psychological harm) to definitely yes (reasons: 'giving back', moral obligation, prevention).[128]
- *Consent for data sharing:* Lay participants discussed the need to give participants the option of blanket/general consent or detailed consent at the time of initial consent.[127] While discussing three different types of consent options (namely broad consent, where participants would be told that their data may be shared with others in the future and the research organisation would decide if sharing is appropriate; middle consent, where participants would be told that data may be shared with people from specific research areas; or explicit consent, where participants would be contacted when there was a request for consent), most respondents favoured broad or middle consent. They suggested qualifiers such as informed participants about the possible data accessors.[84]

- Power imbalances (n=17): Unequal power dynamics were explored across different groups and contexts.
  - *Doctor-patient relationship and therapeutic misconception:* Members of the general public did not appear to be familiar with rules and regulations in relation to biomedical research and felt a sense of hopelessness in relation to tackling medical negligence and violations of participant rights due to the differences in power between doctors and patients ('we are small, they are powerful').[127] This power imbalance and a hierarchical paternalistic relationship, along with a doctor's dual role of caregiver-researcher, influence on patient decision making in trial participation and patients' immense trust in a doctor's judgement, especially when they provided assurance about a new unproven treatment (therapeutic misconception), were reported in qualitative studies.[103,127,140] Authors highlighted these as reasons why the informed consent process should be kept away from the treating physician.[103,127] Therapeutic misconception was also reported as more pronounced amongst those from vulnerable groups (e.g. chronically or terminally ill and from lower socio-economic groups), making them more likely to agree to trial participation.[127]

- *Population groups recruited to trials, informed consent and exploitation:* There was a strong view among representatives from civil society organisations and key informants that trial participants were mainly the poor, from rural and tribal communities, who were easy targets as they had limited financial means to access healthcare on their own.[103,114] There was also some suggestion amongst key informants and contract research organisation staff that this was not by chance but a deliberate attempt to recruit from economically disadvantaged groups in slums, targeting mostly unemployed people for volunteer studies as well as, sometimes, Phase III trials.[103,105,127,140] In a qualitative study with healthy volunteers for bioavailability/bioequivalent studies, there appeared to be a unique equation between the volunteers, the middlemen who recruited them and CRO staff. While all the volunteers were from lower socio-economic groups and stated that the financial incentives were their key motivation for research participation (seen as an alternative career prospect), they were aware of the CRO's dependence on them and were observed demanding higher incentives to join or not quit the study, often with the help of the middlemen who recruited them. Volunteers were observed negotiating a better financial deal for their participation, which was much higher than what was in the protocol and approved by ethics committees.[140] However, nearly every ethics committee member and investigator in a qualitative study denied that it was the poor, unemployed, working class and uneducated who were lured into clinical trial participation due to free treatment or other inducements. Some noted that there was no exploitation as many of their poor and illiterate patients were intelligent and asked decisive questions, while others argued that their participants were not rich or poor, but middle class and well aware of their rights.[90] Some staff from contract research organisations insisted that trials that involved such organisations followed the highest standards and that there was no ethical variability in informed consent processes for trials conducted in India as opposed to the West, as any lack of rigour and diligence would not be acceptable to Western sponsors.[90,115] Representatives from civil society organisations, on the other hand, felt that there was ethical variability between trials in the West and in India, framed within the context of fewer ethical guidelines and regulations in India. They also stated that informed consent was majorly compromised and 'meaningless' when the majority cannot access treatment unless they participated in a trial due the failed public health system.[114] Many investigators (mainly recruited from the private sector) agreed that participants agreed to take part in trials to have better access to physicians and/or medical care.[67]
- *West-East, North-South, developed-developing divide:* Frontline health service providers, including some doctors in a qualitative study were reported as feeling that certain types of research (such as HIV vaccines) were concentrated in third world countries as they would not be acceptable in the West.[112] Most clinical research professionals believed that clinical research between developed and developing countries was inequal.[109] Ethics committee members and representatives from civil society organisations viewed Western pharmaceutical trials that recruited from India as a manifestation of the continuing post or neo-colonialist relationship between Western countries and India.[114,121]
- *Are clinical trials relevant to the needs of India?:* Most investigators (from the private sector in a study conducted by authors employed by a pharmaceutical company), felt that studies were relevant to the needs of India and most also believed that the active comparators used in clinical trials in India were usually the same as in the developing world. However, the majority also agreed that pharma companies should set common research goals for all communities and countries.[67] By contrast, ethics committee members believed that pharma companies were using India as a dumping ground to study drugs that are not required for the country's population.[92] Similarly, some investigators in a qualitative study strongly felt that there was a lack of correlation between the disease burden in India and the type of clinical trials that are conducted in the country. Some of them in leadership roles lamented the lack of requests to conduct trials for tropical diseases (although many suffer or die of them) and the large number of trials for conditions that mirror the disease profile in the West (such as diabetes, heart problems, cancer), which is similar to urban India. They therefore felt that trials conducted in India cater to a small segment of the local population and do not benefit the majority of the population, which is poor.[90] This narrative ran counter to the views of executives from contract research organisations who saw clinical trials as benefitting society and their participation in them being about advancing science rather than the pursuit of financial benefits.[90] Some ethics committee members also opined that foreign sponsors should not be expected to take up responsibility for public health in India when the state had itself failed in their social responsibility of delivering healthcare to the majority of the population.[92]
- *Capacity building:* In a qualitative study with employees of contract research organisations, authors noted that in most trials that they studied, the role of these organisations was focused on downstream activities, merely executing the protocols and agendas set by international pharmaceutical companies, following procedures to do the trials 'right' and meticulous documentation (all as part of the phenomenon described by the authors as big-pharmaceuticalisation), with little evidence of locally relevant innovation and knowledge production. However, despite carrying out tasks central to clinical trials, as these organisations delivered a paid service, they had no intellectual property rights and their names did not feature in trial databases or in publications.[115] Representatives of civil society organisations similarly expressed concerns that Indian researchers and

organisations (terms such as 'servants' 'coolies' and 'implementing agency' were used) merely provided labour to produce global data (terms such as 'pre-cooked research' and 'pre-defined research questions' were used) that benefitted the global North and reinforced existing global hierarchies rather than leading on innovation relevant to the local population. Some noted that the Indian researchers doing the research rarely attain leadership roles and when they do, it appears to take a much longer time to break the glass ceiling.[114]

- *Community engagement in research:* Community advocates reported feeling like they were simply being 'used' by research teams to recruit participants to studies without true engagement in all aspects of research. There was also a general mistrust of authorities/researchers conducting or involved in clinical trials, with some questioning why trials needed to be conducted in their countries.[105]
- *Lay participation in ethics committees:* Two-thirds of ethics committee members with a medical background were in favour of including lay people or patients in committee meetings, while only a quarter of members with non-medical backgrounds were in favour of this. Majority of those with non-medical backgrounds stated that their lack of a medical background did not make them feel restricted from participating during committee meetings.[130] However, two-thirds of clinical research professionals felt that lay people were unable to contribute adequately in ethics committee meetings.[133] Similarly, non-medical, non-scientist members of ethics committees in a public hospital expressed difficulties in participating in committee meetings without adequate training and reported feeling like 'show pieces' with an obligatory presence. Medics and scientist members were reported as being the assertive voices due to the hierarchy between medical and non-medical experts and the technical nature of trial protocols. Additionally, some members mentioned that protocols prepared for the technical (or scientific) committees were presented to ethics committees without any adaption or highlighting of ethical issues.[92] Other key reasons mentioned by clinical research professionals for difficulties faced by lay members of ethics committees were lack of training in GCP, regulations and ethical thinking, inadequate exposure/training in clinical research, human rights and compensation, power imbalances (voice can be easily overturned by experts), being unaware of the importance of their role and being used to merely meet quorum requirements.[108,133] Some non-medical experts (social scientists) noted that not being connected to the institution where the research is to be conducted has its advantages as it is easier for non-affiliated members to raise questions than their clinical colleagues who may fear offending their colleagues/institution, but that they have little power to change things.[92]

- <u>Contract research organisations (CROs), civil society organisations (CSOs) and the clinical trial industry (n=7):</u>
  - *Tracing the growth of CROs in India:* One qualitative study that explored the views of CRO staff in relation to a range of ethical issues in clinical trials, outlined the growth of CROs in India.[115] Participants outlined how the pharmaceutical industry, in the pre-TRIPS period, aimed for self-sufficiency as drugs were required in large numbers and clinical trials were not a priority as the focus was on making generics. However, participants observed that more recently, there has been a move towards biosimilars, which involves producing drugs that are similar to, but slightly different or more advanced than, existing drugs. This move from generic drug manufacturing towards innovative research by local pharma companies (which the authors call 'big-pharmaceuticalisation') was seen as a stepping stone towards the development of new chemical entities (although this was perceived as unaffordable to Indian pharmaceutical companies as the industry was not big enough to afford the millions that developing new entities costs). The authors noted that these accounts of progress were embedded within narratives centred on CRO operations/motives and participant safety, with limited mention of the larger ethical issues such as post-trial benefits for participants, compensation or whether the drugs developed provided therapeutic advantages over existing drugs. There was a feeling that the regulatory landscape in India was slow and did not keep up with the fast-paced growth of clinical trials.[115]
  - *CRO operations and collaborative models:* The same qualitative study outlined participants' accounts of the processes by which international pharma companies contact Indian CROs or international CROs with offices in India to conduct trials. CROs advertise their services on various platforms, including online and in conferences, and approach doctors at private and public hospitals and from those listed on the clinical trials registry of India to act as investigators. Participants also discussed six collaborative models between CROs and sponsors and three different types of trials conducted by CROs.[115] Another qualitative study outlined the process through which middlemen were engaged by CROs to recruit healthy volunteers for bioavailability/bioequivalent studies, creating a pool for participants who were regularly approached for participation (serial participation) and often paid more than agreed in protocol/approved by ethics committees in order to retain their ongoing participation.[140]

- *Malpractice and scandals:* Most CRO staff were critical of the instances of corruption and malpractices amongst CROs reported in the media, but mainly spoke of these as malpractices by 'others' and never themselves – a narrative that the authors found to be vulnerable as at least one CRO in the study was implicated in a widely reported clinical trial controversy in Bhopal[115] (with evidence of malpractice reported in another study on CROs[140]). Also, while participants were not critical of the new regulations introduced in 2013 following the spate of controversies, they were critical of the lack of government support and protection in the wake of media attacks.[115]
- *Motivations of those involved in clinical trials:* Most CRO executives and investigators stated they were not involved in clinical trials for monetary gains but as a service to science, humanity and society, considering that it involved risks and expressed their unhappiness over the media portrayal of the industry.[90] Some activists expressed concerns about ethics committees becoming financially focussed and providing easy approvals to benefit pharma companies.[114]
- *Views on pharma-sponsored clinical trials:* Nearly two-thirds of doctors believed that trials done for academic purposes, including for dissertation purposes, were relatively more ethical and scientific than industry-sponsored trials and that regulations/legislations related to industry-sponsored trials are inadequate. More than half opined that patients are exploited in industry-sponsored clinical trials.[75] Ethics committee members in a qualitative study were concerned about the role of pharma companies in manipulating clinical trial agreements between the sponsor, investigator and institution, to suit their own interests.[92] By contrast, favourable views regarding pharma-sponsored trials were expressed by investigators (mainly from private sector) in a study authored by researchers in a pharma company. They felt that pharma trials addressed the needs of the community, but agreed that the drugs that were developed were eventually unaffordable to majority of the local population.[67] Representatives from civil society organisations saw commercial, industry-driven clinical trials as having a corrupting effect on many fronts – it lured good investigators away from academic research with the promise of financial benefits and contributed towards good research questions being side-lined if they did not have commercial benefits.[114]
- *India as the preferred destination of choice for clinical trials:* CRO executives and investigators felt that India was preferred not just because it was cost-effective to conduct trials in the country and there was a larger proportion of treatment naïve population, but also because of the high quality of work that was produced by Indian researchers. Others offered more practical reasons such as the need for pharma companies to investigate a drug's pharmacodynamics within non-White population groups before they could be sold to them. Some executives and investigators questioned these narratives and felt that the clinical trial industry was not yet established, that India was not as preferred as was originally predicted and that the population was not as treatment naïve as portrayed due to the common use of over-the-counter medications.[90]
- *Role of CSOs in changing the regulatory landscape in India:* A qualitative study traced the role of health social movements in bringing about more stringent regulations (in 2013) to protect trial participants.[114] Members of CSOs drew from interpretations of social justice and emphasised a rights-based approach to health in their accounts of the activism that brought about key regulatory changes. They acknowledged the importance of randomised controlled trials for the advancement of science, but expressed concerns about the disregard for the wider ethical issues (beyond procedural and informed consent focused agendas) and the perpetuation of existing global hierarchies through pharma companies' choice of drugs, conditions and populations being studied. They stated that pharma companies and CROs are known for their lack of ethical oversight if left to themselves. Some members expressed the challenge in being nuanced or balanced in their debates about clinical trials, while being angry at the injustices in the industry. Some activists spoke about the evolution of their views over time from purely ideological to the more pragmatic, to accommodate a need to move away from dichotomous categorisations based on the funding source for trials (Indian and public being good versus foreign and private being bad).[114]

B. Secondary research

B.1. Secondary research: Primarily documentary

Number of studies tagged to topic: 23

Methodological aspects and limitations:

- Documents studied included informed consent documents (n=138, 30, 50, 300, 119),[64,86,95,107,125] insurance documents (n=18),[125] application forms of research projects submitted to ethics committees (n=100, 73, 100, 445),[85,99,118,120] ethics committee site visit reports (n=7),[119] data/records related to research participants (n=42),[110] ethics approval letters (n=20),[123] other ethics committee governance/administration related documentation (such as approval letters, meeting minutes, project registers/files) where the time period of data collection

was mentioned in place of sample size,[66,96] and data from websites of regulatory, accreditation and registration bodies[106,139,141] (note: one of the articles included here is also in section G).[125]

- Reporting practices in journal articles, journal editorial policies and the clinical trial registry in India are also included here.[63,71,74,93,94,124]

Synthesised findings:

- Completeness, errors and quality of data and documentation in research studies (n=6): The most common issues in research application forms submitted to ethics committees were missing or inadequate information in relation to study titles, participant profile, study benefits, key signatures (investigators, patients), budget details, recruitment methods, compensation for participation or study-related injuries, conflicts of interest, patient safety factors, study documentation, duration of study, sponsoring authority and details on informed consent.[85,118,120] Some of these were reported as more common in academic studies (mainly dissertation projects and some investigator-initiated studies) than sponsored studies (mainly industry sponsored and some government sponsored).[120] One study that examined participant data quality and documentation in investigator-initiated and industry-sponsored studies found that accuracy and data completeness were similar across the two groups, except in documentation related to informed consent processes that were somewhat better in industry-sponsored studies.[110] A study investigating ethics approval letters for compliance with regulations noted the common issues as lack of information on ethics committee members who attended the meeting and their designations, absence of legally required quorum (similar to findings in another study[68]) and legal experts, social scientists or ethicists. Similar to studies above, the issues that were raised by ethics committees in these letters were often in relation to patient recruitment methods as well as other issues such as insurance policies and clinical trial agreements.[123] A study that reported findings from seven site visits[119] observed similar issues to those that reviewed research applications forms submitted to ethics committees.[85,118,120] Authors observed inadequate informed consent documentation (such as missing signatures of patients/PIs and use of forms in local languages that had not been approved by the committee) and delays in reporting of serious adverse events.[119]
- Impact of regulatory changes on registration/accreditation status and composition/structure of ethics committees (n=2): A study of governance/administration related documents in two ethics committees found that the regulatory changes of 2013 had an impact on the structure and functioning of the committees. The number of registered studies reviewed remained the same before and after the regulatory changes, but the number of studies approved decreased. However, there was an increase in turnover time. Similarly, the number of serious adverse events that were reported increased, but the number of meetings to discuss these events increased and the committees' income decreased while their expenses increased. There was also more administrative workload and documentation after the changes.[66] A study that aimed to investigate if the 2013 regulations requiring accreditation and registration (and registration renewal every three years) of ethics committees were adhered to, examined information available on national registration and accreditation databases.[106] The study found that most ethics committees registered were institutional with a fifth being independent, but that the registration numbers may not be reflective of the actual number of committees in India. Of those eligible for re-registration, more of the institutional ethics committee (nearly two-thirds of eligible) were re-registered than the independent ones (less than a third of eligible) and of those that applied for accreditation, less than 10% had received it. The study also found that the distribution of committees across different states was skewed (states with similar populations had large variations in committee numbers – for instance Maharashtra and Bihar with similar populations had more than a quarter and less than 1% of all registered committees respectively). Similar issues arose while comparing registered clinical trials and medical colleges against ethics committees per state, with authors noting that this reflected and perpetuated existing health inequalities across states.[106]
- Reasons for uninitiated studies (n=1): Another study that similarly studied the governance/administrative documents from the same two ethics committees as above found that a greater proportion of pharma-sponsored studies were not initiated after queries raised by ethics committees than investigator-initiated ones. Also, the former had mainly ethical queries raised, while the latter had primarily scientific queries raised by the committees. Most of the ethical issues that were not addressed were related to the informed consent document or processes. Key scientific clarifications required were on sample size, eligibility criteria and inappropriate study design, while ethical queries raised by the committees were in relation to the lack of provision of free investigations or treatments/medicines and patient safety concerns. There appeared to be evidence of 'ethics shopping' as some of the uninitiated studies in multi-centric studies were found to be registered on the trials registry (CTRI) as ongoing or completed at other sites in the country, and these had mainly received ethical queries from the original ethics committees.[96]

- Are clinical trials relevant to the needs of India? (n=2): Two audits of the Clinical Trials Registry of India reported that there was a mismatch between the illnesses researched by clinical trials and the country's disease burden.[139,141] Infectious and parasitic diseases rank first in terms of disease burden but 7th in the number of trials registered in that therapeutic area, while nnon-communicable diseases such as cancer and diabetes mellitus, which rank 6th and 13th in relation to disease burden rank high up in the number of trials registered (ranks 1 and 2 respectively).[139]
- Compensation (n=6):
    - *Compensation for participation:* In a study that aimed to investigate the payments allowed for participation in a trial by ethics committees, authors accessed application forms submitted to committees as well as other relevant documents (study protocols, informed consent documents and correspondence with investigators). They found that nearly all observations studies and a third of interventional studies reviewed by three ethics committees over two years had no mention of compensation for participation. Payments by pharma and government sponsored studies were greater than that by investigator-initiated studies. The most common reasons for payment was reimbursement for travel purposes. Committees had no particular policies or standard operating procedures in place for practices regarding compensation for participation and the amount of compensation approved for participation across studies varied hugely. It also appeared that healthy volunteers were paid more than patients.[99] In another similar study, statements about compensation for participation were not mentioned in nearly all academic studies, more than half the government sponsored studies and in about a third of industry-sponsored studies.[120]
    - *Compensation for study-related injuries/serious adverse events (including their management):* In application forms submitted to two ethics committees over a year, statements related to compensation for injury were not mentioned in nearly all academic and government-sponsored studies and in less than a fifth of industry-sponsored studies.[120] Similarly, a study examining application forms submitted to one ethics committee over more than a year found that statements related to compensation provision if risk occurred was not mentioned in all applications.[85] However, a study investigating informed consent documents submitted to one ethics committee over three years found that information relating to compensation for participants for disability/death from research-related injury (Indian GCP-specified) in informed consent documents was improving over time.[107] A similar observation was made in another study that also examined informed consent documents submitted to three ethics committees over seven years. Authors reported that the documents only mentioned compensation for research-related injuries from 2003 (although the guidelines for this existed from 2000), but that the coverage of the issue in informed consent documents increased from 2003 to 2007.[125] In a similar study examining informed consent documents submitted to two ethics committees over two years, a little over a fifth clearly stated there would be no compensation for trial-related injury, while a little less than half made no mention of it, and some provided caveats, restrictions or ambiguous statements.[64]
    - *Compensation for management of study-related injuries/serious adverse events:* The same study also examined the management of trial-related injuries and found that only a third provided clear statements that free treatment will be provided for trial-related injury, less than a third had no statement on the issue and the rest mentioned restrictions on availing free treatment. Authors also found that the two issues, compensation for trial-related injury and for its management/treatment were sometimes mixed together, making it unclear which aspect was referred to.[64] The ambiguity in the language used to describe compensation for management of study-related injuries in informed consent documents and the variations in the type of compensation offered was also mentioned in another study.[125] Authors also found that compensation for study-related injuries was mainly through 'reimbursement' after proving 'causality' (which was in contrast to national guidelines). They also noted that most insurance documents examined had incomplete details and did not always have their terms and conditions explained.[125]
- Informed consent documents (ICDs) – readability and compliance with legal framework and GCP guidelines (n=4):
    - *Readability:* Two studies evaluated the readability of ICDs used in a clinical research site[86] or those submitted alongside research protocols to ethics committees[107] by employing Western readability tests (Flesch Reading Ease Score and Flesch-Kincaid Grade Level Index). One study employed these tests on Hindi ICDs and reported that the reading level was difficult and that it required graduate level education.[86] The other mentioned English, Hindi and Punjabi ICDs in the article, but it was unclear which ones the tests were applied to, and reported that the readability was close to recommended levels and that there were no changes in readability over three years.[107]

- *Compliance with legal framework:* ICDs from one clinical research site were checked for the presence of the mandatory 19 legally required elements (as per Schedule Y). More than two-thirds of the documents were found to deviate from what the law required. The most common areas that were missing were in relation to appropriate alternative treatments and the voluntary nature of participation. All ICDs mentioned that the study was research, the treatment schedule and random assignment of treatment, risks, measures to protect confidentiality and the tests/procedures that the patient must have within the trial.[95]
- *Compliance with GCP guidelines:* ICDs submitted to one ethics committee over three years (divided into two time periods) were evaluated for compliance with Indian GCP guidelines. Compliance increased over time in relation areas such as basic information (aims, methods), benefits/risks and participant rights. In particular, there was an increase in the mention of contact details of research teams, confidentiality of records, right to withdraw, translation to vernacular languages, and compensation for research-related injuries. There was a decrease in mention of free treatment and alternative treatments over the two time periods.[107]

- Reporting practices (n=6): Studies found that a large number of Indian journal articles did not provide information on ethical approval and/or written informed consent from participants and/or guardians in relation to paediatric, psychiatric and HIV/AIDS research.[63,71,74,94] Other areas that were found to be sub-optimally reported were the obtaining of assent (in paediatric research for children over 7 years old),[63] content and language of consent form and process,[71] financial compensation, non-financial benefits,[94] funding source, conflict of interest[93,124] and dual ethical approval (in the case of research sponsored by a high-income country and conducted in India).[74] One study found that although reporting was sub-optimal, it increased over a period of 7 years (2000 to 2007).[71] Another study that evaluated editorial policies of Indian journals for endorsement of CONSORT statement and ICJME requirements, and the reporting quality of randomised controlled trials in Indian journals in relation to CONSORT statement found these to be less than ideal (although the reporting of ethical issues had improved over the years). Authors also found that methodological and ethical issues were better reported in the clinical trials registry in India than in the journals.[124]